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RU–486: DEMONSTRATING A LOW STANDARD FOR WOMEN'S HEALTH?

HEARING

BEFORE THE

SUBCOMMITTEE ON CRIMINAL JUSTICE,
DRUG POLICY, AND HUMAN RESOURCES

OF THE

COMMITTEE ON
GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED NINTH CONGRESS

SECOND SESSION

MAY 17, 2006

Serial No. 109–202

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CONTENTS

Page

Hearing held on May 17, 2006 1

Statement of:
- Harrison, Donna J., M.D., member, Mifeprex Subcommittee of American Association of Prolife Obstetricians and Gynecologists 135
- Patterson, Monty L., Livermore, CA 117
- Rarick, Lisa D., M.D., RAR Consulting, LLC 128
- Snead, O. Carter, associate professor, University of Notre Dame Law School, and former general counsel for the President's Council on Bioethics 338
- Wood, Susan F., former Assistant Commissioner for Women's Health and Director of the Office of Women's Health, Food and Drug Administration 122
- Woodcock, Janet, M.D., Deputy Commissioner for Operations, Food and Drug Administration, U.S. Department of Health and Human Services . 87

Letters, statements, etc., submitted for the record by:
- Cummings, Hon. Elijah E., a Representative in Congress from the State of Maryland, prepared statement of 75
- Harrison, Donna J., M.D., member, Mifeprex Subcommittee of American Association of Prolife Obstetricians and Gynecologists, prepared statement of 137
- Patterson, Monty L., Livermore, CA, prepared statement of 120
- Rarick, Lisa D., M.D., RAR Consulting, LLC, prepared statement of 131
- Ruppersberger, Hon. C.A. Dutch, a Representative in Congress from the State of Maryland, prepared statement of 85
- Snead, O. Carter, associate professor, University of Notre Dame Law School, and former general counsel for the President's Council on Bioethics, prepared statement of 340
- Souder, Hon. Mark E., a Representative in Congress from the State of Indiana:
  - Information concerning lower standards for RU–486 112
  - Judicial Watch Report 3
  - Prepared statement of 69
- Waxman, Hon. Henry A., a Representative in Congress from the State of California, prepared statement of 81
- Wood, Susan F., former Assistant Commissioner for Women's Health and Director of the Office of Women's Health, Food and Drug Administration, prepared statement of 125
- Woodcock, Janet, M.D., Deputy Commissioner for Operations, Food and Drug Administration, U.S. Department of Health and Human Services, prepared statement of 90

RU–486: DEMONSTRATING A LOW STANDARD FOR WOMEN'S HEALTH?

WEDNESDAY, MAY 17, 2006

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY,
AND HUMAN RESOURCES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The subcommittee met, pursuant to notice, at 2:04 p.m., in room 2203, Rayburn House Office Building, Hon. Mark E. Souder (chairman of the subcommittee) presiding.

Present: Representatives Souder, Schmidt, Shays, Cummings, Davis, Watson, Ruppersberger, Norton, and Waxman.

Staff present: Marc Wheat, staff director and chief counsel; Michelle Gress, professional staff member and counsel; Malia Holst, clerk; Karen Lightfoot, minority senior policy advisor and communications director; Sarah Despres, Tony Haywood, Kimberly Trinca, Naomi Seiler, minority counsels; Richard Butcher, minority professional staff member; and Teresa Coufal, minority assistant clerk.

Mr. SOUDER. The subcommittee will come to order. We are here today because there is a drug on the market associated with the deaths of at least 8 women, 9 life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection. There are more than 950 adverse event cases associated with RU–486 out of only 575,000 prescriptions, at most. Adverse events are typically under-reported, since they are offered voluntarily by consumers and health care professionals, so it is most likely that there are many more cases that we don't even know about.

It is very clear that there is a serious problem with RU–486. In failing to address this problem by disguising it, ignoring it, minimizing it, or causing confusion, it is a shameful failure for anyone with the ability and desire to protect women from needless harm.

RU–486 is a common name for Mifeprex. It is produced by Danco Laboratories, a corporate entity located in the Cayman Islands which produces only that single drug and nothing else. Mifeprex is approved by the FDA for the termination of pregnancy through 49 days of development. It is used in combination with another drug called Misoprostol, which causes uterine contractions that expel the dead fetus. This is an off-label use for the Misoprostol, which contains a black box warning against using the drug during pregnancy.

At least five of the deaths following the use of RU–486 have been the result of toxic shock-like syndrome initiated by the bacteria

Clostridium Sordellii. This bacteria is thought to exist in low numbers in the reproductive tracts of many women and is normally combatted by the immune system. Experts in immunology, pharmacology, and maternal-fetal medicine have suggested that because RU–486 interferes with the innate immune response, the bacteria, if present, is allowed to flourish, causing a widespread multi-organ infection in the woman. These infections are not accompanied by a fever and the symptoms match those that are expected after taking the RU–486 regime, including cramping, pain, bleeding, nausea, vomiting. Each of the women infected with C. Sordellii after taking RU–486 were dead within 5 to 7 days.

To investigate the nature of this bacteria, the CDC and FDA held a scientific workshop last week called "Emerging Clostridial Disease." The workshop panelists noted that the rapid growth of the C. Sordellii bacteria in the RU–486 context likely forecloses effective treatment and that there is no currently identifiable window of opportunity for treatment once a woman is infected, even with major interventions such as a hysterectomy. The fatality rate has been 100 percent for the women who have contracted C. Sordellii infection after using RU–486.

Any other drug associated with a 100 percent fatal septic infection that kills otherwise healthy adults within days, with no apparent window for treatment, and associated with an exponential amount of severe reactions would normally prompt an immediate withdrawal. But we are talking about a drug regimen that is administered to cause an abortion, manufactured by a drug company based in the Cayman Islands with no other drugs on the market, and therefore no incentive to voluntarily withdraw its product, no matter how dangerous.

Many abortion advocates feel they have to defend RU–486 because it is an alternative to surgical abortion. However, with eight deaths that we know about, RU–486 is 10 to 14 times more likely to be fatal than surgical abortion during the first 7 weeks of pregnancy, the period during which the drug is administered. To continue defending this dangerous drug in light of the mounting scientific evidence, injury, and death is to allow one's zeal for abortion to truly distort their view about what is right for women's health. The 10-times-more-deadly danger posed by RU–486 should not be considered an acceptable risk that justifies keeping this drug on the market.

The approval of RU–486 was made under extreme political pressure from the Clinton administration, which is well documented in a recent report by Judicial Watch entitled "The Clinton RU–486 Files." I ask that this report be included in the hearing record.

[The information referred to follows:]

A Judicial Watch Special Report:
The Clinton RU-486 Files

◆

The Clinton Administration's Radical Drive to Force an Abortion Drug on America

Judicial Watch, Inc. ♦ 501 School Street, S.W. ♦ Washington, D.C. 20024
Tel: 202-646-5172 ♦ Fax: 202-646-5199 ♦ www.JudicialWatch.org

Introduction

This Judicial Watch Special Report analyzes newly uncovered documents from the National Archives at the Clinton Presidential Library in Little Rock, Arkansas, describing the Clinton administration's radical drive to introduce the abortion drug RU-486 (mifepristone) into the American marketplace.

The records include the Clinton administration's legal, political and press strategies for rushing RU-486 through the Food and Drug Administration (FDA) processes, despite the manufacturer's historical refusal to permit marketing the drug here. The legal, political and press memos articulate the Clinton administration's views regarding various players in the drug approval and marketing process -- women's groups, members of Congress, public interest groups and the media.

Judicial Watch has engaged in a five-year legal battle with the FDA for release of records under the provisions of the Freedom of Information Act (FOIA), 5 U.S.C. §552, concerning RU-486. We uncovered over 9,300 pages of documents and 840 Adverse Event Reports pertaining to the abortion drug. To date, the deaths of at least six women have been attributed to RU-486. The FDA scheduled a scientific conference for May 11, 2006 in order to study the controversial abortion drug and the circumstances leading to the deaths.

Judicial Watch promotes transparency, integrity and accountability in government, politics and the law. We make aggressive use of open records and open meetings laws as a means to obtain documents with which to educate the American public on the operations of their government and to hold public officials accountable. Judicial Watch also provides technical, research and litigation assistance to public interest groups interested in obtaining information about government activity which may not have the necessary resources or experience to pursue information on their own as part of the Judicial Watch Open Records Project.

Thomas Fitton
President
Judicial Watch, Inc.

April 26, 2006

Questions or comments concerning this report should be directed to:

Christopher J. Farrell
Director of Investigations & Research
Judicial Watch, Inc.
501 School Street, SW -- Suite 500
Washington, DC 20024
Tel: 202-646-5172
cfarrell@judicialwatch.org

The Clinton RU-486 Files:
The Clinton Administration's Radical Drive to Force an Abortion Drug on America

Executive Summary

During a February 2006 research trip to the National Archives at the Clinton Presidential Library, Judicial Watch uncovered new records detailing the Clinton administration's rush to market the abortion drug RU-486 (mifepristone) to American women. The documents include political, legal and press strategy memoranda from Health and Human Services (HHS) Secretary Donna Shalala, FDA Commissioner, Dr. David Kessler, and HHS Chief of Staff Kevin Thurm. Some of the memoranda are addressed to the White House -- in particular, Carol Rasco, the Clinton administration Director of Domestic Policy.

Analysis of the records shows:

- President Clinton ordered HHS and FDA to coordinate and promote the marketing of RU-486 as his first official act in office.
- Within one month, the FDA Commissioner had met with the RU-486 manufacturer and their parent company.
- Official U.S. Government political, economic and diplomatic pressure was brought to bear to strong-arm the companies into changing their policies in order to make the drug available in the United States.
- The FDA was compromised in its role as objective reviewers of the safety and efficacy of the drug.
- The five standard requirements for certifying a drug "safe and effective" were circumvented to rush RU-486 to market.
- Radical, pro-abortion extremists dominated the Clinton administration's "women's health care" agenda and their reckless drive to bring RU-486 to America ultimately cost at least six women their lives and the lives of over 560,000 unborn children.

The Clinton RU-486 Files:
The Clinton Administration's Radical Drive to Force an Abortion Drug on America

* * *

"Hoechst has historically refused to permit Roussel Uclaf to seek marketing approval for RU-486 as an abortifacient in the United States. Both Dr. Kessler [FDA Commissioner] *and I have taken steps to persuade Roussel Uclaf and Hoechst to change their position."*

Donna Shalala
Health & Human Services Secretary
Clinton Administration
November 15, 1993
Confidential Memo to White House

* * *

In February 2006, Judicial Watch uncovered previously confidential files and working papers from the holdings of the National Archives at the Clinton Presidential Library in Little Rock, Arkansas that provide remarkable insight into the Clinton administration's relentless drive to market RU-486 (mifepristone), a drug used to cause abortion, to American women. The documents offer a window into the political strategy, legal theories and media "spin" on the Clinton administration's abortion program.

RU-486 was first developed in France in 1981. It is a manmade steroid designed to work against the hormone progesterone, which is required to promote a baby's proper growth and development. RU-486 works to chemically destroy the unborn child's environment, cutting off nourishment and starving the baby to death in the mother's womb. A second chemical, misoprostol, is then used to create cramping and contractions to expel the dead baby from the mother's womb. The "procedure" must begin within 49 days of conception. The Clinton administration considered this method of abortion part of "women's health care." President Clinton thanked the maker of RU-486 in writing, "On behalf of the government of the United States and for the women of America. . ."[i]

On January 22, 1993, in his first official act, President Clinton issued a memorandum directing HHS Secretary Donna Shalala to promote the testing and licensing of RU-486 in the United States. (See Tab A)

Abortion was a key domestic policy item for President Clinton. RU-486 was just one part of the overall strategy for his administration's agenda. For example, in a

National Archives document entitled, "President William J. Clinton -- Eight Years of Peace, Prosperity and Progress," the first "accomplishment" listed reads:

> **Abolished Restrictions on Medical Research and the Right to Choose** As his first executive actions, President Clinton revoked the Gag Rule, which prohibited abortion counseling in clinics that receive federal funding to serve low-income patients. He also revoked restrictions on a woman's legal right to privately funded abortion services in military hospitals, restrictions on the import of RU-486, and restrictions on the award of international family planning grants (the "Mexico City Policy"). The President also lifted the moratorium on federal funding for research involving fetal tissue, allowing progress on research into treatments for Parkinson's disease, Alzheimer's, diabetes and leukemia. (Executive Memoranda, 1/22/93)[ii]

The tone was set for the Clinton administration's drive towards promoting abortion as "health care." Shalala and FDA Commissioner, Dr. David Kessler, engaged in a political, legal and economic campaign to force the French pharmaceutical firm, Roussel Uclaf, and their German parent corporation, Hoechst, A.G., to file a "new drug application" (NDA) with the FDA, and begin marketing RU-486 to American women.[iii]

In April 1993, the FDA brokered a meeting between Roussel Uclaf and the Clinton administration's anointed abortion proponent, the Population Council, a non-profit organization that conducts research on so-called "reproductive health issues." Roussel Uclaf and the Population Council already had an existing contractual relationship concerning provision of abortifacients (substances that induce abortion) for various clinical trials.[iv] It is difficult to understand the FDA's role in bringing the parties together, other than to continue to bring official U.S. government pressure on Roussel Uclaf and to designate the Population Council as the Clinton administration's abortion drug development and marketing proxy.

The Population Council claims to be ". . . an international, nonprofit, nongovernmental organization, seeks to improve the well-being and reproductive health of current and future generations around the world and to help achieve a humane, equitable, and sustainable balance between people and resources."[v] The organization was founded by John D. Rockefeller III in 1952. In 2005, they projected spending over $71 million in 70 countries around the world. Their work is funded by governments, foundations, individuals and "multilateral organizations."[vi]

According to the Clinton RU-486 files, Roussel Uclaf made the decision to use the Population Council as the administration's surrogate for forcing RU-486 on America.

There is no mention in the memoranda of Planned Parenthood or the National Abortion and Reproductive Rights Action League (NARAL). There is no mention of public disclosure, discussion, competition or bidding. One might imagine a selection process or staff discussion of the relative pros and cons for selection of another abortion group, but there is no evidence of any such discussion or consideration. In a memo by HHS Chief of Staff Kevin Thurm (discussed in detail below), the Clinton administration seems to have been predisposed to using the Population Council to carry out their abortion plans based on an existing relationship of the abortion non-profit with the maker of RU-486.

Roussel Uclaf repeatedly sought total U.S. government-sponsored indemnification from any damages it might incur by bringing RU-486 to the U.S. marketplace. Roussel Uclaf President, Dr. Edouard Sakiz, specifically expressed concerns over liability actions against his firm "if a woman had an incomplete abortion and delivered a deformed fetus." Dr. Sakiz was also particularly concerned about "consequential damages," such as the economic costs from boycotts. The Clinton administration's fervent commitment to making RU-486 part of the American abortion industry is demonstrated through Dr. Sakiz's reservations concerning legal and economic exposure. The Clinton administration's near-obsession with introducing a "safe and effective" abortion drug is revealed in Shalala's confidential memo to the White House of November 15, 1993:

> "Dr. Sakiz's view was that if the United States Government wanted RU-486 to be marketed in the United States, it should compensate Roussel Uclaf for any damages that the company might suffer from complying with the United States Government's request."

(See Tab B)

Dr. Sakiz was saying, in other words, "If you want it so badly, you pay the consequences." The Clinton administration was attempting to trump a business decision of the pharmaceutical company while exposing the corporation to risk for abiding by a U.S. government request.

Even Clinton FDA Commissioner Kessler understood and memorialized the controversy over the administration's aggressive efforts to introduce RU-486 when he wrote in a September 30, 1993 memorandum to Shalala:

> ". . . other Congressional members have written to Hoechst expressing their strong opposition to the marketing of RU-486 in this country. This, and the well-publicized activities of anti-abortion groups, have provided Hoechst and Roussel Ucalf with evidence that the U.S. population

> lacks cohesiveness on this issue and that the abortion debate continues."

(See Tab C)

The Clinton administration realized that attempting to enact blanket indemnification by the U.S government of a foreign corporation for an abortion drug was politically and practically impossible. According to the Clinton RU-486 files, Dr. Sakiz still went ahead and committed to negotiating with the Clinton administration surrogates – the Population Council – agreeing:

- To license RU-486 to the Population Council which would conduct a clinical trial involving 2000 women pursuant to an investigational new drug application;
- The Population Council would ultimately submit an NDA to the FDA based on the results of the clinical trial and on other studies conducted by Roussel Uclaf; and
- The Population Council, with the concurrence of Roussel Uclaf, would chose a new manufacturer for the drug, and that Roussel Uclaf would transfer its technology for making the drug to that manufacturer because Roussel Uclaf did not want to manufacture the drug for sale in this country. [Emphasis added.]

(See Tab B)

According to the Clinton RU-486 files, over the next few months Roussel Uclaf reiterated its desire for protective federal legislation providing blanket indemnification from the use of RU-486. Roussel Uclaf did not anticipate any profit from selling RU-486 in the United States; and was only entering the American market at the insistence of the Clinton administration. FDA representatives told Roussel Uclaf that such protection was extremely unlikely.

In a September 30, 1993 memorandum to Shalala, FDA Commissioner Kessler recounts a conversation he had with Jim Boynton, legal counsel for the Population Council, concerning the Roussel Uclaf indemnification legislation. Kessler pointed out the recent passage of the Hyde Amendment (restricting federal funds for abortion), and that with one exception (swine flu event), the United States had never agreed to indemnify any drug manufacturer. Apparently sensing that it might be perceived as inappropriate for the FDA commissioner to be discussing indemnification with a drug company representative for a supposedly safe drug, Kessler tried to cover his tracks. Kessler wrote that he, ". . . further explained that it would go far beyond FDA'S appropriate role to seek such protection for a drug company." [Emphasis added.] Nonetheless, the FDA offered to advance the idea within HHS.

Not satisfied with the denials of indemnification from the FDA and HHS, in September 1993 Roussel Uclaf hired legal counsel (reportedly, Lester Hyman and John Hoff of the firm Swidler & Berlin) to lobby the federal government for indemnification "at levels higher than the FDA" – presumably from President Clinton and other pro-abortion advocates in the Congress, such as Rep. Ron Wyden and Rep. Henry Waxman. Concerned with these moves, HHS Chief of Staff Kevin Thurm and HHS General Counsel Harriet Rabb initiated a meeting with attorneys from Swidler & Berlin. During that meeting Roussel Uclaf's lawyer suggested that the United States could exercise its statutory powers of eminent domain and seize the patent for RU-486 for the abortifacient uses of the drug.[vii]

Meanwhile, the Population Council and Roussel Uclaf pressed forward with licensing details, and simultaneously made plans to sway the leadership of Hoechst to allow their subsidiary to enter into an agreement with the Population Council. Shalala's confidential memo to the White House warns, ". . . we do not think the negotiations will be successfully concluded without pressure on Roussel Uclaf/Hoechst."[viii]

Shalala suggested the Clinton administration bring the force of the United States Government to bear on the Hoechst and Roussel Uclaf corporations. She also went on to suggest that the United States exercise its international diplomatic and economic pressure on the German and French governments, as a means of further "influence" against the corporations. In a November 15 confidential memo to the White House, Shalala wrote: "The French and German governments might be displeased to learn that their companies are not accommodating a request made by the United States Government."

While the Clinton administration pondered exercising the full economic and diplomatic weight of the United States Government to advance its abortion agenda, it is important to note that Roussel Uclaf was willing to give a royalty-free license to any major U.S. pharmaceutical company – but no U.S. company would take the license.

The Clinton RU-486 files show specualtion among administration officials concerning delays in the negotiations between Roussel Uclaf and the Population Council. The pending retirement of the chief executive officer of Hoechst, Professor Wolfgang Hilger, was discussed in Kessler's September memo, noting that Prof. Hilger was "very staunchly Catholic." There was also a discussion of the likelihood of an international foundation being created by the drug's inventor, Dr. Etiene Balieu, for broader marketing opportunities. Apparently the Clinton administration was concerned about competition from an abortion drug "insider."[ix]

Just as the name of the Population Council "appeared" in the Clinton administration's confidential memos without a trace of how it became the administration's surrogate, so too does the recommendation for Felix Rohatyn to serve as an "expert advisor."[x]

After a review of the economic, political and diplomatic issues involved in strong-arming Hoechst and Roussel Uclaf, Dr. Kessler advanced Mr. Rohatyn's name by concluding with a political point: "We think that someone familiar to these circles would advance the Administration's goal to bring a safe and effective abortifacient to the U.S. market." Again, there is no discussion, alternatives or explanation offered for this appointment. The question of appointment of an "expert advisor" for the U.S. government is raised and answered in the space of one paragraph.

In a remarkable admission that the FDA had been thoroughly politicized in the Clinton administration's radical drive for RU-486, the agency's commissioner, Dr. Kessler, wrote in his September memo, ". . . the FDA cannot take this issue too far without compromising its role as objective reviewers of the safety and efficacy of the drug."

The Clinton RU-486 file offering the most comprehensive treatment of the administration's strategic campaign to introduce RU-486 to the American market is a memorandum dated May 11, 1994 from HHS Chief of Staff Kevin Thurm to the White House – in particular, Carol Rasco, Director of the Clinton administration Domestic Policy Council. (See Tab D)

Thurm's memo details three issues submitted for decision by the President:

- Whether the President is willing to write a letter to the maker of RU-486, asking that the U.S. patents for the drug be assigned to a non-profit entity in this country [Population Council].
- If the negotiations between Roussel Uclaf and the Population Council fail, and the "only" available option is the "gift offer," is the U.S. Government willing to accept the RU-486 patent rights, and under what conditions?
- If the government is not willing to accept the patent rights, what will be the basis for that decision, and how will it be communicated to the American public?

Thurm develops and discusses each of the factors bearing on the subject in a series of tabs and exhibits to his memo. He provides a history and background tab recounting the Clinton administration's position on RU-486; a tab discussing legal issues;

a brief marketing study addressing timing, administration, and abortion proxies; political considerations; and finally, a discussion of press strategies and concerns.

Thurm explains that on April 26, 1994, the Board of Roussel Uclaf passed a resolution authorizing the assignment of RU-486 patent rights to either the U.S. Government or to a non-profit organization. If the rights were to go to a non-profit organization [Population Council], then Roussel Uclaf demanded a letter from the President of the United States requesting RU-486 on behalf of the women of the United States. President Clinton signed exactly such a letter on May 16, 1994. (See Tab E)

President Clinton's extraordinary letter is direct documentary evidence of his personal intervention as a politician, and clear evidence that the RU-486 patent rights would never have been assigned to the Population Council without his compliance with Roussel Uclaf's demands.

President Clinton's RU-486 request letter to Dr. Edouard Sakiz of Roussel Uclaf claims that it is important for the women of the United States to have "safe and effective medical treatments." Under that rubric, President Clinton writes that he "understands" Roussel Uclaf has been in negotiations with the Population Council. Of course, the Population Council had been serving as a Clinton administration abortion "front" for several months. President Clinton closes his RU-486 request letter by stating: "On behalf of the government of the United States and for the women of America, I thank you for your work."

Thurm's memo specifically addresses the requirements for RU-486 clinical trials and the Population Council's requirements for marketing application for the FDA. The significance of speedy approval and abbreviation of various timelines is a theme throughout his analysis. Not surprisingly, the Clinton administration's radical drive to bring RU-486 to the American market manifested itself in other ways, once the patent rights were obtained by the Population Council. For example, the five standard requirements for certifying a drug "safe and effective" were circumvented to rush RU-486 to market.[xi] Probably the most reckless act by the FDA was the waiver of the normal requirement for random, double-blind, control tests for new drugs. The FDA's expedition in this process was justified with language reserved for drugs developed to cure life-threatening conditions. Certainly, pregnancy is not a disease, nor is it likely to be life threatening – so how could they have twisted the rules so dramatically? What political pressure was brought to bear?

The "political issue discussion" tab to Thurm's memo offers a glimpse into the Clinton administration's abortion politics techniques. The Clinton administration steadfastly continues the manipulation of language that seeks to forever separate the words "kill," "baby" and "abortion." Thurm states: "It is, therefore, extremely important that the decision concerning RU-486 be placed in the context of promoting women's health and maintaining the close relationship of the administration to these ["pro-choice" and women's groups] groups."

The Clinton administration wanted a quick victory on RU-486 and was deeply concerned that RU-486 might remain a "front burner" issue through the 1996 presidential election. They were particularly sensitive to the prospect of prolonged, intense, public attention and debate on RU-486. Thurm advised political caution concerning unintended consequences, allowing " . . . Republicans and others opposed to the administration to focus attention on this decision and its aftermath."

The Clinton press strategy documents discuss the ramifications of accepting or rejecting the gift of the RU-486 patents. Acceptance of the patent gifts was relegated to Secretary Shalala "on behalf of American women," but specifically as a means of "insulating the White House." While seeking insulation, the press memo stresses the need to credit President Clinton for keeping his campaign promises and giving a major "reproductive rights victory" to American women. The memo also contains a disturbing directive:

> " . . . there should also be a concerted effort on the part of HHS Public affairs team to place stories that outline the hurdles that must be overcome to shield the Administration against fallout from our allies in the event efforts to get RU-486 to the market become stalled in bureaucratic process, in Congress or for other reasons."[xii]

If the Clinton administration's RU-486 strategy failed all together, it appears the press response included a calculated scenario for resorting to lying to the American public. Working through the various scenarios, the author of the memo offers an "alternative":

> " . . . another potential argument we could embrace is the position that we wanted more than the rights they were willing to grant because our interest in this drug goes beyond the issue of abortion, the need for which we are committed to making as rare as possible."[xiii]

Still worried about potential fallout and damage with abortion proponents and allied political groups, the press memo ends stating:

> "Without a doubt, a 'no' will subject the Administration to a firestorm of protest by pro-choice and women's groups; and there will be few natural political allies vocally defending this decision, particularly in light of the relative difficulty of explanation.'[xiv]

Beyond the Clinton Files -- RU-486 in 2006

As Judicial Watch reviewed the Clinton RU-486 files, documenting the extraordinary lengths the administration went to rush the abortion drug to U.S. markets, the earliest correspondence on file at the Archives caught our attention and, in hindsight, provided some perspective for examining RU-486 matters in 2006. (See Tab F)

The file contained a handwritten letterhead note from Betsey Wright, President Clinton's former Chief of Staff, and the White House staff member charged with covering-up "bimbo eruptions." The note reads: "To Carol Rasco. This just got forwarded to me. Please handle. BW 3/9/93." There is an additional notation that reads: "cc for Shalala on Tues. MK," with the name Shalala circled and a line drawn to the words "To handle."[xv]

Betsey Wright's note was attached to a letter dated January 6, 1992, from Ron Weddington, an attorney that served as co-counsel in the infamous *Roe v. Wade* lawsuit. Weddington attached an "open letter" to President-elect Clinton. Weddington's letter recommends that the new president should, " . . . start immediately to eliminate the barely educated, unhealthy and poor segment of the country . . ." and that the " . . . government is going to have to provide vasectomies, tubal ligations and abortions . . . RU-486 and conventional abortions."[xvi]

Weddington states: "Condoms won't do it. Depo-Provera, Norplant and the new birth control injection being developed in India are not a complete answer, although the savings that could be effected by widespread government distribution and encouragement of birth control would amount to billions of dollars."

The full text of Weddington's letter is a breathtakingly arrogant exegesis on the abortion lobby's culture of death. As disturbing as the Weddington letter is to read, what is more disturbing is the fact that Betsey Wright, one of President Clinton's closest confidantes, tasked Donna Shalala to "handle" it along with the Director of the White House Domestic Policy Council, Carol Rasco. Weddington's ravings were not relegated to a file for unsolicited constituent correspondence. On the contrary, the Weddington letter is, chronologically and philosophically, the foundation document for the Clinton RU-486 files.

Today we are faced with the horrible results of the political and "health care" campaign to put RU-486 on the market. Since RU-486 was approved for use in the United States in September 2000, at least six women have died after taking the abortion drug. Only after the death of 18 year old Holly Patterson, on September 17, 2003, did the media and the FDA begin to pay attention to the dangers of RU-486.

In November 2004, following the third woman's death, the FDA elected to "strengthen the warning notice," a step that may have provided some sort of "informational" or disclaimer insulation for the FDA, but a tactic that certainly did not make RU-486 any safer for women.

Planned Parenthood, which had ignored the FDA's warnings concerning how to administer the drug regimen, played a role in the deaths of four women as the "procedure" provider. The FDA has determined that the four California women who died after taking RU-486 all suffered from a highly lethal bacterial infection -- Clostridium sordellii. The bacterium flourishes in the uterus and then enters the bloodstream, eventually leading to toxic shock.

It is quite likely that more women have died from RU-486 and their deaths have gone unreported because doctors, medical examiners and coroners are not obligated to forward reports dealing with RU-486 side effects to the FDA. This is particularly true in cases where local health officials may not associate a death with an RU-486 abortion, especially if the woman's death occurs several days or even weeks later.

Even abortion providers now have low regard for the safety of RU-486. Dr. Warren Hern, an abortionist in Denver, Colorado has stated: "I think surgery should be the procedure of choice." Pills, he said, "are a lousy way to perform an abortion." He is not alone. Dr. Damon Stutes, an abortionist from Reno, Nevada reluctantly agrees with Pro-Life critics of RU-486, stating, "the truth is the truth," and that, "The complications from RU-486 far exceed the complications of surgical abortion." [xvii]

It seems that the federal government has finally come to grips with the growing number of deaths attributed to the use of RU-486 and is prepared to take some action, however late. The government will convene a scientific conference at the Center for Disease Control in Atlanta, Georgia on May 11, 2006. More than two dozen scientists and doctors will make presentations concerning the deadly bacterial infections that killed the California women mentioned above.

Conclusion

Judicial Watch hopes that this special report on the Clinton RU-486 files has provided the reader with sufficient documentary evidence from primary sources to illuminate the Clinton administration's rush to achieve part of its abortion agenda through bringing RU-486 to America. Armed with the long-delayed facts from Clinton insider memoranda, the reader is now equipped to evaluate policy and hold public officials accountable.

On September 28, 2000, the day RU-486 was approved for U.S. markets, the FDA Commissioner, Dr. Jane E. Henney, said in an interview, "Politics had no role in this decision."[xviii] The public now has copies of the the Clinton RU-486 files that unequivocally say otherwise.

Endnotes

[i] See Tab E: Letter from President William J. Clinton to Dr. Edouard Sakiz, Chaiman of Roussel Uclaf, dated May 16, 1994.

[ii] See: http://clinton5.nara.gov/media/pdf/eightyears.pdf

[iii] Hoechst had a historical reason for wanting to keep a low profile concerning RU-486. Hoechst was part of a cartel connected to the infamous I.G. Farben Chemical Company, the makers of Zyklon-B -- the cyanide gas used in Nazi death camps. In 1999, Hoechst merged with another European pharmaceutical company to form Aventis.

[iv] Copies of the Roussel Uclaf – Population Council contract were not available from the Archives.

[v] See: http://www.popcouncil.org/about/index.html

[vi] See: http://www.popcouncil.org/mediacenter/PC_Key_Facts.html

[vii] See Tab C: FDA Commissioner Kessler's Memorandum to HHS Secretary Shalala, dated September 30, 1993.

[viii] See Tab B: HHS Secretary Shalala's Confidential Memorandum to White House Director of Domestic Policy Carol Rasco, dated November 15, 1993.

[ix] See Tab C, pages 4-5.

[x] Felix Rohatyn is a Wall Street investment banker and served as President Clinton's Ambassador to France from 1997 to 2000.

[xi] Donna J. Harrison, M.D., "Dangerous Medicine," *The New York Times*, November 19, 2004.

[xii] See Tab D: HHS Chief of Staff Kevin Thurm's Memorandum to White House Director of Domestic Policy Carol Rasco, Subject: RU-486, dated May 11, 1994; Tab 5: Press Strategies and Concerns.

[xiii] *Ibid.*

[xiv] *Ibid.*

[xv] See Tab F: Clinton Transition Team Director of Public Outreach Betsey Wright's correspondence file Re: RU-486 from Mr. Ron Weddington, dated 3/9/93.

[xvi] *Ibid.*

[xvii] Gardiner Harris, "Some Doctors Voice Worry Over Abortion Pill's Safety," *The New York Times*, April 1, 2006.

[xviii] Gina Kolata, “U.S. Approves Abortion Pill; Drug Offers More Privacy, and Could Reshape Debate, *The New York Times*, September 29, 2000.

Tab A

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THE WHITE HOUSE
WASHINGTON

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

In Import Alert 66-47, the Food and Drug Administration ("FDA") excluded the drug Mifepristine -- commonly known as RU-486 -- from the list of drugs that individuals can import into the United States for their "personal use," although the drugs have not yet been approved for distribution by the FDA. (See FDA Regulatory Procedures Manual, Chapter 9-71.) Import Alert 66-47 effectively bans the importation into this Nation of a drug that is used in other nations as a nonsurgical means of abortion.

I am informed that in excluding RU-486 from the personal use importation exemption, the FDA appears to have based its decision on factors other than an assessment of the possible health and safety risks of the drug. Accordingly, I hereby direct that you promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. Furthermore, if the FDA concludes that RU-486 meets the criteria for the personal use importation exemption, I direct that you immediately take steps to rescind Import Alert 66-47.

In addition, I direct that you promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 or other antiprogestins.

You are hereby authorized and directed to publish this memorandum in the Federal Register.

William J Clinton

Tab B

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

NOV 15 1993

~~CONFIDENTIAL~~

file

4/14/04

MEMORANDUM FOR CAROL RASCO

The purposes of this memorandum are: (1) to inform you of the Department's progress in implementing the President's directive of January 22, 1993, to "assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 or other antiprogestins;" and (2) to outline the necessary next steps to accomplish the President's directive.

Background: You may recall that RU-486 is manufactured by the French firm Roussel Uclaf and is approved to induce abortions in France, the United Kingdom, and Sweden. Roussel Uclaf has stated that it can act in the United States only with the approval of its parent company, Hoechst AG, a German firm. Hoechst has historically refused to permit Roussel Uclaf to seek marketing approval for RU-486 as an abortifacient in the United States.

Both Dr. Kessler and I have taken steps to persuade Roussel Uclaf and Hoechst to change their position. In February Dr. Kessler met with Dr. Edouard Sakiz, the President of Roussel Uclaf, to discuss the availability of RU-486 in the United States for research and marketing. In March I wrote to Professor Wolfgang Hilger, President of the Board of Hoechst, to ask him to permit Roussel Uclaf to begin any necessary testing of RU-486 in the United States in preparation for filing a new drug application with the FDA. Later in March there were press reports that Roussel Uclaf would respond to the requests of the Clinton Administration to make RU-486 available in this country and that testing of the drug would begin approximately two months later (i.e., in May).

In April 1993, FDA arranged a meeting between Roussel Uclaf and the Population Council, a non-profit corporation that conducts research on reproductive health issues. The meeting's purpose was to facilitate an agreement between those parties to work together to test RU-486 and file a new drug application for the drug. The Population Council was identified as the most likely group to work with Roussel Uclaf because of an existing contract between these two parties that required Roussel Uclaf to give the Population Council sufficient amounts of the drug for the Population Council to conduct clinical trials. The contract also appeared to require Roussel Uclaf to license the drug to the Population Council if Roussel Uclaf were unwilling to sell the drug in the United States.

At the April meeting, Dr. Edouard Sakiz, President of Roussel Uclaf, raised the issue of federal legislation to indemnify

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Roussel Uclaf from any damages it might incur by permitting RU-486 to be marketed in the United States. Dr. Sakiz was worried about product liability actions against Roussel Uclaf if a woman had an incomplete abortion and delivered a deformed fetus. Dr. Sakiz was also concerned about consequential damages, such as the economic costs from boycotts of other Roussel Uclaf or Hoechst products, or bombings of Roussel Uclaf/Hoechst facilities by right-to-life groups. Dr. Sakiz's view was that if the United States Government wanted RU-486 to be marketed in the United States, it should compensate Roussel Uclaf for any damages that the company might suffer from complying with the United States Government's request.

Dr. Sakiz was clearly informed at the April meeting that such legislation would never be enacted and that the FDA would not support Roussel Uclaf in seeking it.

Despite being told that there was no possibility of obtaining federal legislation to protect Roussel Uclaf from consequential damages or product liability suits, Dr. Sakiz committed Roussel Uclaf to negotiate with the Population Council to bring RU-486 onto the United States market. Specifically, at the April meeting Roussel Uclaf and the Population Council agreed:

- That Roussel Uclaf would license RU-486 to the Population Council, which would conduct a clinical trial involving 2000 women pursuant to an investigational new drug (IND) application;

- That the Population Council would ultimately submit a new drug application (NDA) to FDA, based on the results of the clinical trial and on other studies that have been conducted by Roussel Uclaf; and

- That the Population Council, with the concurrence of Roussel Uclaf, would choose a new manufacturer for the drug, and that Roussel Uclaf would transfer its technology for making the drug to that manufacturer because Roussel Uclaf does not want to manufacture the drug for sale in this country.

It was then left for the Population Council and Roussel Uclaf to revise the terms of their contract, while Roussel Uclaf began sending scientific information to FDA and the Population Council. A tentative goal of September 15 was established for concluding the contract negotiations. As of late July 1993, the Population Council thought that the negotiations were proceeding smoothly, though slowly.

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CURRENT STATUS

On August 2, 1993, the Population Council's lawyer notified FDA that **Roussel Uclaf had recently reasserted its demand for protective federal legislation.** Roussel Uclaf insisted that the Population Council obtain a commitment from the United States Government that: 1) legislation would be enacted making it a crime for any person to hurt or harass any doctor administering RU-486, their patients, or the drug's manufacturers, distributors, and salespersons; 2) the Department of Justice publicly commit to enforce this law, if enacted; 3) legislation would be enacted indemnifying Roussel Uclaf for any product liability exposure resulting from the use of RU-486 in this country, or, as an alternative, a prohibition of any product liability actions against Roussel Uclaf for RU-486; 4) as part of any legislation, indemnification for consequential damages.

In exchange Roussel Uclaf would give the Population Council a royalty-free license because it has decided to forego any profit from entering the United States market. **In short, Roussel Uclaf's position is that it should not incur any liability exposure as a result of making RU-486 available in this country** as an abortifacient because it does not anticipate any profit from selling RU-486 for that use in the United States and is entering the American market only at the request of the United States Government. Roussel Uclaf remains willing to exploit its patent for non-abortifacient uses of RU-486, should any other use be found to be safe and effective.

FDA advised the Population Council's lawyer that it could not make a commitment to seek such legislation and that its enactment was extremely unlikely, both for political reasons and because the United States had never agreed to indemnify any drug manufacturer, with the exception of the swine flu precedent. The FDA also communicated that seeking such protection for a drug company far exceeded FDA's appropriate role, but that the agency would discuss the situation with the Department.

In mid-September Roussel Uclaf hired legal counsel, Swidler and Berlin, to lobby the federal government at levels above FDA to obtain the legislation described above. On October 5, Kevin Thurm, the Department's Chief of Staff, and Harriet Rabb, the Department's General Counsel, met with lawyers from Swidler and Berlin to discuss the situation. The Department initiated the meeting to assess how the United States Government might facilitate successful completion of the negotiations between Roussel Uclaf and the Population Council. At that meeting, the company reiterated its concerns about obtaining indemnification for potential losses and was again told emphatically that the Department would not support its efforts to obtain federal legislation. Roussel Uclaf's lawyer then suggested that the

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United States could exercise its statutory powers of eminent domain and take over the patent for RU-486 insofar as it covers abortifacient uses of the drug.

The Population Council appears to be attempting to meet those demands of Roussel Uclaf that do not require the enactment of federal legislation. We have been advised by the Population Council that they sent a proposed licensing agreement to Roussel Uclaf on October 11, although we do not know whether Roussel Uclaf and Hoechst will find this proposal acceptable. In addition, the Population Council's President recently met with the President of Roussel Uclaf, and is planning to send a delegation to Germany during the first few weeks of November in the hope that if Hoechst understands that the Population Council is a serious, credible organization, Hoechst will withdraw its objections and permit Roussel Uclaf to enter into an agreement with the Population Council. Despite these moderately positive developments, we do not think that the negotiations will be successfully concluded without pressure on Roussel Uclaf/Hoechst.

Moreover, we have learned that Hoechst is interested in using an American venture capitalist group as a partner for the Population Council; this group is thought to be able to secure funds sufficient to indemnify Hoechst at the level it desires. However, it is our understanding that the Population Council appears unwilling to work with this group. This issue has further complicated the negotiations.

AVAILABLE OPTIONS TO MOVE FORWARD NEGOTIATIONS

The negotiations between Roussel Uclaf and the Population Council have not been successfully concluded because of the insistence of Roussel Uclaf and Hoechst that they be protected from all economic harm if they permit RU-486 to be marketed in this country. There are two options for moving forward the stalled negotiations:

One option is to enlist the aid of Felix Rohatyn, or someone of comparable stature, to negotiate with Roussel Uclaf and Hoechst on behalf of the United States Government. The negotiations require a person with extensive experience in the international business community, especially France and Germany. In addition the person must understand the pharmaceutical industry and have the standing to participate in high-level discussions that might involve appropriate ambassadors, as well as the Health Ministers in France and Germany.

A second option is for the United States to exercise its statutory powers of eminent domain and take over the patent for RU-486, insofar as it covers the abortifacient use of the drug. The Government could then contract with a company to manufacture

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and distribute the drug. As noted above, this option was suggested by Roussel Uclaf's lawyers in their October 5 meeting with the Department's Chief of Staff and is clearly the company's preferred approach. While the United States government has the legal authority to take over the patent, such an approach is rare and in this case is politically complex. Although legal, there are particular concerns about the political viability of this approach and the willingness of Congress to permit such an action to stand. We note that Roussel Uclaf did not demand that the governments of France, England, or Sweden take such steps.

NEXT STEPS

Unless you object, the Department plans to engage the services of Felix Rohatyn or someone comparable as a negotiator. This negotiator would require the State Department's support in making appropriate diplomatic contacts, both with the United States Ambassadors to France and Germany, the French and German Ambassadors to this country, and other high-level officials in France and Germany, such as the respective Health Ministers. The purpose of such contacts would be to assess the situation and determine what measures the United States could take to persuade Roussel Uclaf and Hoechst to make RU-486 available in the United States. The French and German governments might be displeased to learn that their companies are not accommodating a request made by the United States Government. In addition, a negotiator of Felix Rohatyn's caliber might identify means other than federal legislation to satisfy Roussel Uclaf's and Hoechst's concerns.

In order for the negotiator to succeed, the Department and the Administration must be unequivocal in the position that taking over the patent for RU-486 is not an option. To avoid any ambiguity on this point, the negotiator should have a letter signed by the Secretary of Health and Human Services making clear on behalf of herself and the Administration that the United States government will not take over the patent. In addition the letter should request on behalf of the Administration that Hoechst and Roussel Uclaf conclude negotiations for the entry of RU-486 onto the U.S. market expeditiously. Roussel Uclaf will have every incentive to delay the negotiations if it thinks that the United States will ultimately take over the patent. It is the Department's position that this option should be unambiguously rejected, not only because it is controversial, but because its continued existence will make it impossible for the negotiator to obtain any other agreement.

Donna E. Shalala

Tab C

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

September 30, 1993

NOTE TO: The Secretary

FROM: The Commissioner of Food and Drugs

SUBJECT: RU-486

On January 22, 1993, President Clinton issued a memorandum directing you to assess initiatives to promote the testing, licensing, and manufacturing in the United States of RU-486 (mifepristone).[1] The Agency has had ongoing dialogue with Roussel Uclaf to get a marketing application submitted to FDA for the drug. Both you and the FDA are on record as stating that if RU-486 is a safe and effective alternative to surgical abortion, then women in the U.S. should have access to that drug. The President also directed you to reassess whether RU-486 qualifies for importation under FDA's personal use importation policy.[2]

I. Current Marketing of the Drug

RU-486 is manufactured by the French firm Roussel Uclaf and it is approved to induce abortions in France, the United Kingdom, and Sweden. Roussel Uclaf has stated that it can act in the United States only with the approval of its parent company, Hoechst AG. Hoechst has historically refused to permit Roussel Uclaf to seek marketing approval for RU-486 as an abortifacient in the United States. Both you and I have asked Hoechst to permit Roussel Uclaf to file a new drug application (NDA) for the drug. Hoechst remains adamant in its refusal. While some members of Congress have written to Hoechst urging the company to

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[1] Although there are several investigational new drug applications (INDs) on file with FDA for RU-486 for other uses, including Cushing's syndrome, diabetes, meningioma, and breast cancer, Roussel Uclaf will not pursue marketing applications for these indications until the abortion issue is resolved. FDA representatives have met with representatives from the National Institutes of Health (NIH) to discuss initiatives to promote the testing in the United States of RU-486 and other antiprogestins. NIH is limited in what it can do by the restrictions placed on its appropriation by the Hyde Amendment.

[2] In accordance with the President's January 22 memorandum, FDA has reassessed whether RU-486 might qualify for importation under FDA's personal use importation policy and whether the import alert should be rescinded. There are significant public health implications associated with rescinding the import alert, especially related to whether the drug could be safely used under these circumstances; the availability of counterfeit RU-486 on the world market for which the Agency cannot attest to purity, quality, or safety; and the fact that Roussel Uclaf's RU-486 is so tightly controlled as to be unavailable for personal importation even if the import alert were to be rescinded. The Agency submitted its recommendation on this issue to PHS on July 14, 1993. Because the import alert has been challenged by a woman who attempted to bring a small quantity of RU-486 into the country, the Agency is working with the Department on an appropriate response to this ongoing litigation.

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submit a marketing application for RU-486, other Congressional members have written to Hoechst expressing their strong opposition to the marketing of RU-486 in this country. This, and the well-publicized activities of anti-abortion groups, have provided Hoechst and Roussel Uclaf with evidence that the U.S. population lacks cohesiveness on this issue and that the abortion debate continues.

II. Summary of Discussions with Roussel Uclaf Regarding Testing of the Drug

In April 1993, FDA arranged a meeting between Roussel Uclaf and the Population Council to attempt to get those parties to agree to work together to test RU-486 and file a new drug application for the drug. The Population Council was identified as the most likely group to work with Roussel Uclaf because the Population Council had a contract with Roussel Uclaf which required Roussel Uclaf to give the Population Council sufficient amounts of the drug so that the Population Council could conduct clinical trials. The contract also appeared to require Roussel Uclaf to license the drug to the Population Council if Roussel Uclaf was unwilling to sell the drug in the United States. A copy of that contract, which must remain confidential, is attached.

At the April meeting, Dr. Edouard Sakiz, president of Roussel Uclaf, raised the issue of federal legislation to indemnify Roussel Uclaf from any damages it might suffer from permitting RU-486 to go onto the United States market. Dr. Sakiz was worried about product liability actions against Roussel Uclaf if a woman had an incomplete abortion and a deformed fetus. Dr. Sakiz was also concerned about consequential damages, such as the economic costs from boycotts of Roussel Uclaf (or Hoechst) products, bombings of Roussel Uclaf/Hoechst facilities, etc. by right-to-life groups. Dr. Sakiz's view was that if the United States Government wanted RU-486 on the U.S. market, then the United States Government should make Roussel Uclaf whole for any damages Roussel Uclaf might suffer because it had agreed to the United States Government's request.

Dr. Sakiz was told quite clearly at the April meeting that such legislation would never be enacted and the FDA would not support Roussel Uclaf in its advancement of that idea.

Despite being told that there was no possibility of obtaining favorable legislation, Dr. Sakiz committed Roussel Uclaf to go forward with the Population Council to bring RU-486 onto the United States market. Specifically, at the April meeting Roussel Uclaf and the Population Council agreed:

- That Roussel Uclaf would license RU-486 to the Population Council, which would conduct a clinical trial involving 2000 women pursuant to an investigational new drug (IND) application;

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o That the Population Council would ultimately submit an NDA to FDA, based on the results of the clinical trial and on other studies that have been conducted by Roussel Uclaf; and

o That the Population council, with the concurrence of Roussel Uclaf, would choose a new manufacturer for the drug, and that Roussel Uclaf would transfer its technology for making the drug to that manufacturer, because Roussel Uclaf does not want to manufacture the drug for sale in this country.

It was then left for the Population Council and Roussel Uclaf to revise the terms of their contract, while Roussel Uclaf began sending scientific information to FDA and the Population Council. The contract negotiations continued from sometime after the April meeting until recently. As of late July 1993, the Population Council thought the contract negotiations were proceeding smoothly, though slowly. In those negotiations the Population Council was represented by Jim Boynton of Christy and Viener and Roussel Uclaf was represented by Joe Orsini, its corporate council in Paris.

On August 2, 1993, Jim Boynton, the Population Council's lawyer, notified FDA that Roussel Uclaf had recently demanded that the Population Council obtain a commitment from the U.S. Government that the U.S. would enact legislation that would protect all persons who had anything to do with RU-486. This was described as similar to "right-to-access" legislation that would make it a crime for any person to hurt or harass any doctor administering RU-486, their patients, and the manufacturers, distributors, and salespersons for the drug. Roussel Uclaf also demanded that the Department of Justice promise to expend its resources to enforce this law, if enacted. Roussel Uclaf also asked for legislation that would indemnify Roussel Uclaf against any product liability exposure as a result of the use of RU-486 in this country or, as an alternative, that would ban any product liability actions against Roussel Uclaf for RU-486. Finally, Roussel Uclaf asked for legislation that would indemnify Roussel Uclaf against consequential damages. Roussel Uclaf's principal assertion is that it is willing to give the Population Council a royalty-free license, because it has decided (given a push by Hoechst), that it will forego any monetary gain from entering the U.S. market. In short, because Roussel Uclaf does not expect to make any money off of RU-486 in the U.S. market, and sees itself as permitting RU-486 to enter the U.S. market only because asked to do so by the United States Government, then it should not incur any liability exposure on account of the drug.

FDA advised Mr. Boynton that the FDA could not make a commitment to seek such legislation, pointing out that Congress had recently reenacted the Hyde Amendment and that other than the swine flu situation, the United States had never agreed to indemnify any drug manufacturer. The FDA further explained that it would go far beyond FDA's appropriate role to seek such protection for a drug company. The FDA offered to advance the idea within the Department, but was advised by Mr. Boynton that the answer given was sufficient.

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In mid-September, Roussel Uclaf hired legal counsel (allegedly, Lester Hyman and John Hoff of Swindler and Berlin) to lobby the federal government at levels above FDA to obtain legislation protecting the company from potential losses, as described above.

III. Analysis

The FDA's principle objection to Roussel Uclaf's request for indemnification and related relief has been pragmatic--we did not (and do not) think Congress would ever pass such legislation. Having said that, we also think that there are other policy reasons for refusing to seek indemnification of a drug manufacturer, for example:

- It would create an unacceptable precedent for any manufacturer of a significant vaccine or drug to seek indemnification as a condition for bringing the product to market. There is little basis to distinguish RU-486 from a breakthrough AIDS drug or unique vaccine. The swine flu indemnification plan proved very problematic for the United States Government.
- If public health problems were to occur post-approval, the interest of the United States as an indemnifying party would be to disprove that problems had occurred, while FDA's obligation would be to objectively investigate and take appropriate actions to protect the public health. This would be an untenable conflict for the United States Government.

Roussel Uclaf's liability and boycott concerns should not be underestimated. Because Roussel Uclaf is willing to give the Population Council a royalty-free license, it wants to eliminate any potential for expenses due to the drug's introduction into the United States market. Roussel Uclaf has also expressed its willingness to give a royalty-free license to any other major U.S. pharmaceutical company, but has found no company willing to take the license. Roussel Uclaf could, possibly, sell the drug to the Population Council (or to others) but it appears unwilling to do so, perhaps because the drug may have important other therapeutic benefits in the future, and it may want to maintain the right to sell to those markets. However, Hoechst may be willing to simply abandon the patent or give it to the United States.

There are some that suggest that Roussel Uclaf is simply playing a delaying game--waiting until the very staunchly Catholic Hoechst CEO (Prof. Wolfgang Hilger) retires in April 1994--so that then Roussel Uclaf would be free to exploit the drug in the United States and elsewhere for all uses. Others suggest that Roussel Uclaf does not want to reach agreement with the Population Council, but is merely stalling until an international foundation is created by Dr. Etienne Balieu, the inventor of the drug and a former Roussel Uclaf employee, to which Roussel Uclaf could then sell the rights to the drug.

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The speculation is fueled by the essentially unanswered question--as to why Roussel Uclaf is willing to manufacture and sell RU-486 to some markets (England, France, and Sweden) but not to others (e.g., the United States). The common thinking is that Hoechst is only willing to permit Roussel Uclaf to sell RU-486 in a country when Hoechst is forced to do so politically, and, therefore, the only way to get RU-486 onto the U.S. market is to exercise political pressure on Roussel Uclaf and on Hoechst.

This thinking appears borne out by the circumstances here--Roussel Uclaf was willing to come to the table (at FDA) when it had received pressure from President Clinton (the January 23, 1993, Executive Order), you (your March 12, 1993, letter to Prof. Hilger at Hoechst), and FDA, but that since that pressure has waned the incentive to come to an agreement has also waned.

Another possibility is that the Population Council is simply attempting to reach an agreement that leaves Roussel Uclaf with too little, and that if the Population Council were willing to settle for less (e.g., the ability to study, but not to market the drug or to indemnify Roussel Uclaf) then a deal could be reached.

IV. Recommendation for Expert Advisor

This situation calls for someone of Felix Rohatyan's caliber for several reasons. At the outset, we must make it clear that the FDA cannot take this issue too far without compromising its role as objective reviewers of the safety and efficacy of the drug. But equally as important is the fact that this is an issue where business and politics intersect quite dramatically. Because of the abortion debate, Roussel Uclaf is left alone to promote its drug. Other major U.S. drug manufacturers have, to date, refused to join forces with Roussel Uclaf--either by agreeing to go forward with their own abortifacient drug products, or by agreeing to be the manufacturer or distributor of RU-486. Therefore, Roussel Uclaf feels isolated (and vulnerable) by the U.S. demands. It will take an experienced person, familiar with the drug industry, to sort out these issues.

Second, there are pragmatic, economic concerns to be faced. Roussel Uclaf's concerns about indemnification are realistic concerns that need to be satisfied. Someone with extensive experience in the business community (in France and Germany as well as in the United States) will have a better understanding of the various ways this concern can be overcome.

Finally, there are diplomatic issues that may need to be addressed. It may be that France and Germany would be unhappy to learn that their companies were not accommodating a request made by the United States Government. The U.S. Ambassadors to France and Germany will

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need to be consulted on these issues, and your counterparts in France and Germany may also need to be involved. We think that someone familiar to these circles would advance the Administration's goal to bring a safe and effective abortifacient to the U.S. market.

Mary Pendergast
for David A. Kessler, M.D.

Attachment: Contract

cc: Dr. Philip Lee
Mr. Kevin Thurm

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THE WHITE HOUSE
WASHINGTON

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

In Import Alert 66-47, the Food and Drug Administration ("FDA") excluded the drug Mifepristine -- commonly known as RU-486 -- from the list of drugs that individuals can import into the United States for their "personal use," although the drugs have not yet been approved for distribution by the FDA. (See FDA Regulatory Procedures Manual, Chapter 9-71.) Import Alert 66-47 effectively bans the importation into this Nation of a drug that is used in other nations as a nonsurgical means of abortion.

I am informed that in excluding RU-486 from the personal use importation exemption, the FDA appears to have based its decision on factors other than an assessment of the possible health and safety risks of the drug. Accordingly, I hereby direct that you promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. Furthermore, if the FDA concludes that RU-486 meets the criteria for the personal use importation exemption, I direct that you immediately take steps to rescind Import Alert 66-47.

In addition, I direct that you promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 or other antiprogestins.

You are hereby authorized and directed to publish this memorandum in the Federal Register.

William J. Clinton

Tab D

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MAY 11 1994

TO: Carol Rasco

FROM: Kevin Thurm

SUBJECT: RU 486

Background

Roussel Uclaf, a French subsidiary of the German company, Hoechst, holds two United States patents for its product, RU 486, which has abortifacient and potentially scores of other medical uses. The French company has engaged the Population Council, a not-for-profit organization, in over 14 months of negotiations designed to transfer Roussel Uclaf's United States patent rights to the Population Council which would then take steps to bring RU 486 to market in this country. Those negotiations are on-going.

On May 9, 1994, Roussel Uclaf wrote a letter to Secretary Shalala stating the company's wish, instead, to offer the RU 486 United States patent rights to the American government insofar as the abortifacient and other gynecological uses are concerned. The company proposes voluntarily to assign its patent rights, as so limited, to the government free of charge, asking nothing in return.

Were the government willing to accept the "gift" offer, negotiations with the Population Council would be discontinued, and the patents, as so delimited, would be made available for assignment to the United States.

Alternatively, Roussel Uclaf has advised that should its bilateral negotiations with the not-for-profit be resolved, the deal cannot be finally closed unless and until the President of the United States writes a letter to the French company asking, on behalf of the women in America, that the patents be assigned to a non-profit entity in this country.

Roussel Uclaf strongly favors the gift to the government arrangement. Your advisors strongly favor the bilateral arrangement and have taken steps consistently and firmly to so insist.

Issues for Decision

One: Whether the President is willing to write a letter to the manufacturer of RU 486 asking that the United States patents for that product be assigned to a not-for-profit entity in this country. A suitable letter might read as follows:

> It is important for the health of women in the United States that they have access to the widest possible range of safe and effective medical treatments. In support of

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> that goal, in January 1993, I asked the Secretary of Health and Human Services to promote the testing and licensing of mifepristone [RU 486] and other antiprogestins in the United States.
>
> To permit the appropriate testing, development and distribution of RU 486 in the United States, I ask that your company give its mifepristone patent rights in the United States to a non-profit organization that would take all necessary steps to file a new drug application with the Food and Drug Administration [FDA], so that the FDA can determine whether the drug is safe and effective for use in the United States.

Two: If the bilateral negotiations between Roussel Uclaf and the not-for-profit entity fail, and the only option then currently on the table is the gift offer, is the government of the United States willing, and if so, under what conditions, to accept the offer of the patent rights for RU 486?

Three: If the government is not willing to accept the offer of the patent rights, on what is that decision to decline based, and how will it be communicated to the American people?

* * * * * * * * * * * * * *

The following tabs set forth discussion of the various factors that may be brought to bear on the decision-making:

Tab 1:	History and background of RU 486 in this Administration
Tab 2:	Legal issues
Tab 3:	Bringing RU 486 to market [timing, available entities, administrative hurdles]
Tab 4:	Political considerations
Tab 5:	Press strategies and concerns

The following documents are attached for your reference;

Exhibit 1:	The President's Memorandum of January 22, 1993
Exhibit 2:	Roussel Uclaf's May 9, 1994 letter to Secretary Shalala attaching a draft offer of the gift
Exhibit 3:	Roussel Uclaf's draft letter to the President
Exhibit 4:	Minutes in French and translation of the April 26, 1994 Roussel Uclaf board meeting setting out the need for a letter from the President

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BACKGROUND

Roussel Uclaf, a French subsidiary of the German company, Hoechst, holds two United States patents for its product RU 486, which has abortifacient and various other medical uses. The patents will expire in the years 2000 and 2001. Hoechst, the parent company, is co-owned by the Celanese Corporation, whose direct or indirect product lines include Nike sneakers and seat belts; the company does about $8 billion worth of business per year in the United States.

On January 22, 1993, the President directed the Secretary to "assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU 486 or other antiprogestine" (Exhibit 1). Within the month, the FDA, through Commissioner David Kessler, requested both Roussel Uclaf and Hoechst to expedite the process and met with representatives of Roussel to discuss issues. In March 1993, Secretary Shalala wrote to the president of Hoechst urging him to eliminate all corporate barriers to introduction of RU 486 in the United States.

Roussel Uclaf identified the Population Council, a non-profit organization based in New York, as the most likely vehicle through which to produce, distribute and test RU 486; the two parties have a 1982 contract which gives the Population Council some limited rights to license Roussel Uclaf product in this country.

Over the past fourteen months, the two parties have conducted on-again/off-again negotiations over a distribution scheme, liability insurance (product and damage to property), and insurance for lost profits due to economic boycotts of non-related products. During these talks, Roussel, in addition to the three main issues, occasionally raised subsidiary matters; these bumps in the road served to delay the negotiations (some believe that Roussel was in a holding pattern in anticipation of corporate leadership changes in January and April of this year). In several newspaper stories on this issue during this period, representatives of the two parties have been quoted saying they expected a deal shortly. Obviously this has yet to materialize.

Last fall, lawyers representing Roussel Uclaf met with HHS officials to discuss ways the federal government might help the negotiations. Over a series of meetings, the corporation's lawyers presented a variety of requests, including whether the Administration would seek legislation indemnifying Roussel for all potential damages or would seize the patents. HHS officials repeatedly told Roussel's lawyers that neither was a possibility, and that the deal should be done through the private parties.

On April 14, 1994, the Secretary, along with other HHS officials, met with representatives of the two parties, including Professor

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Ernst Afting (current CEO of Roussel), Dr. Edouard Sakiz (past CEO and current Board Chair of Roussel), and Margaret Carlson (head of the Population Council). The Secretary stated that the U.S. government would neither seek legislation indemnifying Roussel nor seize the patents. She made clear to the parties the importance she attached to the introduction of the product in the U.S. through an agreement between them. She ended the meeting by imposing a May 15, 1994 deadline for successful completion of their negotiations.

In light of this deadline and hearings scheduled by Congressman Ron Wyden for 10:00 a.m. on May 16 to obtain a status report, the parties have continued their negotiations. Although many issues have been resolved, some remain: the extent of insurance coverage for product liability and damage to property, and a "pull the plug" option which would give Roussel the authority to require the Population Council to withdraw the product from the market if the potential liability from all lawsuits exceeded a specified amount.

On April 26, 1994, the Board of Roussel Uclaf passed a resolution authorizing under certain circumstances the assignment of patent rights to either the United States government or to a non-profit organization (Exhibit 4). If the rights are to be given to a non-profit, the President of the United States must so request by letter on behalf of the women of the country (see draft letter in cover memo).

By letter of May 9, 1994, Roussel notified the Secretary that it was prepared to assign the patent rights (for abortifacient and other gynecological uses) to the government and attached a draft letter to the President from Professor Afting, the president and CEO of Roussel (Exhibits 2 and 3). This draft letter closely mirrored an earlier informal draft discussed with Kevin Thurm, Harriet Rabb and David Kessler during the prior week.

Discussions between the parties are scheduled to continue through the end of the week. If the private arrangement is not concluded, we must be prepared to have an answer to Roussel's letter which we believe the company would send (or at least publicize). There is some "buzz" among pro-choice and women's groups about this issue so there is a chance developments will leak before the deal is finished or the letter is formally sent.

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LEGAL ISSUES DISCUSSION

I. **Gift Acceptance.** The first question is whether the government should insist that any gift be for all known medical uses, not just abortifacient and gynecological [including, perhaps, "morning after"] uses. On the one hand, the broader rights may make the patent more attractive to potential licensees. On the other hand, some potential licensees may be appropriate repositories of the government's patent rights for the designated uses, but not the full range of known medical uses. Finally, the burden of testing and bringing forward the product for abortifacient and gynecological uses may be more than enough obligation. The responsibility of pursuing research and testing on all the known medical uses to bring the promising ones to fruition may be more than the government and any licensee want to assume.

The Secretary has statutory authority to accept a gift, such as a patent, on behalf of HHS's Public Health Service. Alternatively, the directors of the national research institutes at HHS's National Institutes of Health (NIH) have statutory authority to accept gifts to support the activities of their institutes. Each option has pluses and minuses.

A. Secretarial gift acceptance. Because patents are intangible property, by statutory directive, the evidence of the gift (in this case, the original patent assignments), must be lodged with the Department of the Treasury. Treasury has the discretion to hold the property or liquidate it at HHS's request. There is unlikely to be a problem raised by Treasury, but, to date, that Department has had no part in the RU 486 issue and must be consulted should this route be chosen.

B. NIH gift acceptance. No involvement of Treasury is required. Gifts to NIH institutes must be made to support the activities of the receiving institute - so a showing of such purpose would have to be made. This is not likely to pose a problem, but no work has been done to identify a likely institute recipient or to prepare the gift justification.

Finally, with regard to gift acceptance, since Roussel Uclaf is an entity doing business with HHS, including specifically the Public Health Service and its components, the government will have to be sure that accepting the gift does not give rise to a public perception concern. There is no ethical impediment to accepting gifts from entities so positioned, but care must be taken to weigh the benefits and consequences so that the public can be assured that no favor has been curried or promised. In fact, it has not.

II. **Transfer of the Gift.** Roussel Uclaf has offered to assign its rights to the abortifacient and gynecological patent uses to the government. Were the United States to accept the assignment

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from Roussel Uclaf, the government would in turn find a licensee or licensees willing and able to take responsibility for obtaining FDA approval and bringing the product to market. Although it is conceivable that the government could perform these tasks itself, only the Department of Defense now manufactures drugs on a large scale.

Since, by law, federal agencies are authorized to grant licenses in federally owned patents, were the government to have the patents by assignment, subsequent licensing arrangements are possible. Additionally, patent law provides the patent owner (or, in this case, the patent assignee) with the right to sue for patent infringement. Such capacity to bring suit could be consequential if counterfeit product began to appear in the United States.

III. **Licensing the United States Patent Rights.** Government agencies are authorized by law to grant non-exclusive, exclusive or partially exclusive licenses under federally-owned patents. Licenses to PHS-owned inventions are negotiated by the NIH Office of Technology Transfer in accordance with government-wide regulations.

Under the regulations, non-exclusive licenses can be given by the government relatively easily and directly to any applicants, generally speaking, whose capacity to act responsibly regarding the license has been demonstrated.

Exclusive or partially exclusive licenses are subject to a different, but not much more difficult process. Notice of the patent's availability must be published in the Federal Register, and a sixty day period for filing written objections must be allowed. No less than three months after the date of publication, and after consideration of any objections received, an exclusive or partially exclusive license may be granted. In that event, the agency must make determinations regarding the necessity for an exclusive license, rather than a nonexclusive one, the effect of the license on competition, and whether small business firms have been given first preference in accordance with the statute and regulations.

If and once the United States accepts the gift, it will be critically important that some bidder(s) come forward seeking a license to bring the product to market. Roussel Uclaf's efforts to shop this product around to United States pharmaceutical companies to get one or more to take up the responsibility of bringing RU 486 to market have been unsuccessful. Roussel Uclaf reports that the reluctance reflects other companies' unwillingness to bear (i) the product liability risks associated with the abortifacient or (ii) the political pressure from anti-abortion forces.

IV. **Possible United States Tort Liability.** The likelihood of United States tort liability depends, in large measure, on the

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government's role in bringing RU 486 to market. Through sovereign immunity, the United States government is not subject to liability except to the extent that it consents to be sued. The Federal Tort Claims Act (FTCA) is a statutory limited waiver of sovereign immunity and, thus, acts as consent to being sued. Under the FTCA, the government is liable for personal injury caused by the negligent or wrongful act or omission of a Federal employee under circumstances where the government, if a private party, would be liable to the plaintiff. It would be unlikely for a court to allow a suit to go forward against the government under the FTCA if the government merely performed the "discretionary functions" of accepting a gift, licensing the patents, and acting on an application for FDA to approve a drug.

However, were the government to become enmeshed in facilitating or playing a direct role in the transfer of the technical background information that makes it possible actually to make RU 486, for example, the government risks being drawn into liability. An approach which limits the government's role in bringing RU 486 to market, while solving the lion's share of the potential government liability risk, creates other problems. Without the backup technical "know how," it would be years before any government licensee could create the product. Since it is unlikely that a licensee would bid for these patent rights without the actual prospect of bringing the product into existence, the United States could be left holding the patents with no licensee willing to step up and take them.

Alternatively, if a European or other off-shore manufacturer made the product in a fashion that meets FDA standards, the product is potentially importable by a government licensee. One wrinkle on this process results from the technology transfer regulations referenced above which note that normally, licensees of United States patents have to agree that the product will be produced substantially in the United States.

In short, to the extent the government refuses to become involved in actually transferring the technology, tort liability is kept at bay. But licensees may be kept at bay as well, leaving the government holding the patents with no prospect of bringing RU 486 to the women in America.

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BRINGING RU 486 TO MARKET

A. Direct Patent Transfer to Population Council

If Roussel Uclaf agrees to license its patent rights in RU 486 to the Population Council, the Population Council would then have to take the following steps:

- Locate a drug manufacturer that would be willing to manufacture RU 486 for the United States market (we are advised that such a manufacturer has been identified by the Population Council).

- Obtain information from Roussel Uclaf on how Roussel Uclaf manufactures RU 486 and on its testing of the drug, so that the new manufacturer could follow parallel processes and the Population Council could refer to Roussel Uclaf's animal and human testing of RU 486 in any submission to the Food and Drug Administration. If Roussel Uclaf provides this information and technology transfer, it will significantly shorten the amount of time it will take to bring the drug to the United States market (assuming the drug is found to be safe and effective by FDA). With Roussel Uclaf's information, it might take six to twelve months for the Population Council's manufacturer to begin production of the drug, and for the Population Council to file its marketing application with the FDA. If Roussel Uclaf refuses to provide such information, it will take the Population Council eighteen months to two years to begin production, and up to five years to repeat the animal and human tests that show whether the drug is safe and effective.

Roussel Uclaf has stated that they will transfer the technology to the Population Council, but we do not consider this a strong assurance.

- Begin some clinical testing of the drug in the United States. Clinical trials, though not absolutely necessary for FDA approval, would permit women in the United States to have access to the drug, and for United States physicians to become familiar with the drug, while the Population Council prepared its marketing application for the FDA.

If Roussel Uclaf were to provide French-made RU 486 to the Population Council for the clinical trials, such trials could begin in the United States in approximately six months (five months for the Population Council to design its trials and find physicians willing to do the trials, and one month for FDA approval). If Roussel Uclaf were not willing to provide the drug for clinical trials, such trials would have to wait until (1) the Population Council's manufacturer could begin production of the drug, and (2) either Roussel Uclaf gave the Population Council its animal studies or the Population Council did its own animal studies.

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Roussel Uclaf has stated that it would provide the French-made RU 486 to the Population Council for the clinical trials, but again we do not consider this a strong assurance.

o File a marketing application with the FDA. As indicated above, if Roussel Uclaf provides information and transfers its technology to the Population Council, a marketing application could be filed with the FDA within six to twelve months. FDA review would take no longer than six months. Many of the scientific decisions on the proper use and distribution of the drug have already been considered by the FDA, based on information already provided to FDA by Roussel Uclaf and the Population Council. Roussel Uclaf would not need to finish its United States clinical trials before filing a marketing application with FDA; such trials could be used to refine the use of the drug at a later time.

B. Patent Transfer to the United States

If Roussel Uclaf gives its patents to the United States, the United States would have to take the following steps:

o The United States would have to determine the scope of the rights given to the United States -- are the rights only in the abortifacient and other gynecological uses of the drug, or in all uses of the drug (e.g., gynecological uses, Cushing's disease, breast cancer).

o The United States would then need to transfer its rights in the patents to a third party. This process is discussed at Tab 2, and would take at least six months.

o The license holder would then need to take all of the steps outlined above, i.e., find a manufacturer, conduct the necessary tests, and file a marketing application with the FDA. The length of time these steps will take depends on whether Roussel Uclaf is willing to transfer its information, technology, and the drugs necessary for clinical trials to the license holder. Roussel Uclaf has advised the government that it would provide the information and French-made RU 486 for clinical trials to the United States' licensee, but it could change its mind.

It is difficult to determine whether the United States's license holder would take appreciably longer to bring RU 486 to market than the Population Council would need if the Population Council received a direct transfer of rights from Roussel Uclaf. Obviously, if the United States licensee is the Population Council, little time will be lost above that associated with the transfer of the patent rights from the United States to the Population Council. If another group becomes the United States's

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licensee, that group might be able to bring the drug to the United States market slightly faster than the Population Council (if the group chosen was very familiar with the drug, had a good manufacturing facility, the cooperation of Roussel Uclaf, experience in FDA marketing applications, and excellent contacts with United States physicians) or much slower (if the group falls short on any factor).

We anticipate that if Roussel Uclaf gives its patent to the United States, it will add at least six months, and quite possibly twelve to eighteen months, onto the time needed to bring the drug to the United States market. This estimate excludes any additional time generated by litigation (see Tab 2).

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POLITICAL ISSUE DISCUSSION

In viewing the various options, it is important to place them in a broader political context, particularly as they relate to health care reform, given the likelihood that Congress will narrow the current Health Security Act provisions that provide for abortions under pregnancy-related services.

Because of this situation with the Health Security Act, the introduction of RU 486 will be of greater significance to the pro-choice and women's groups. If the Administration is viewed as closing the door or rejecting an apparently reasonable offer on RU 486, then the path toward reaching a non-confrontational agreement with the advocates on the Health Security Act could become much more difficult. It is, therefore, extremely important that the decision concerning RU 486 be placed in the context of promoting women's health and maintaining the close relationship of the Administration to these groups.

With regard to other political considerations, the acceptance of RU 486 by the federal government, as opposed to by a private non-profit organization, would most certainly lead to a floor amendment on the Labor, HHS appropriations bill, or other legislative vehicle to prohibit federal funds from being used in conjunction with RU 486. It is difficult to predict the exact nature of the amendment. However, in the last Congress, Representatives Dornan, Dannemeyer, Lent, Bartlett, Bunning and Hunter co-sponsored a bill to prohibit federal funds from being used for clinical studies of RU 486 as an abortifacient. Given the likelihood of another Hyde-type amendment on the House and Senate floors this year, as well as the expected abortion-related amendments on health care reform, the members of the House and Senate will be frustrated at having to face another abortion-related vote (on RU 486 appropriation limits). The outcome of such a vote is difficult to predict.

To date, we have worked very cooperatively with Congressman Ron Wyden, the chief Congressional advocate in providing access to RU 486 to women in this country. We expect to be able to continue this close working relationship through the upcoming hearing on May 16. Because Congressman Wyden has postponed past hearings, and is very frustrated by the fourteen months of negotiations, it is unlikely that he would be willing to postpone the May 16 hearing. He is convinced that Roussel Uclaf and Hoechst have been stalling for time, and that it is important to remain firm on the hearing date in order to force agreement or to make it clear to the American public that the companies have no intention of providing RU 486 to the American market.

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Finally, regardless of the precise wording of the President's January 22, 1993 memorandum, the expectation it created among the pro-choice and women's groups is that the federal government will do everything possible to get RU 486 introduced in this country. Leaders of these groups will be concerned with Administration action on health care reform and other issues, including the choice to replace Justice Blackmun. Saying "no" to a facially reasonable offer by Roussel Uclaf weakens our political base and may subject the President to criticism that he is not sticking to his original position.

Given the expression of Presidential support for RU 486 in January 1993, a "yes" adds marginal political cost (separate from issues like health care reform). For 1996 purposes, we probably lose few friends and anger few voters not already positioned on this or related issues.

A "yes", however, also means the Administration will have this issue on its front burner for a significant period of time. Anticipated floor amendments in Congress, rallying at HHS or other government buildings by pro-life groups, and the necessarily public process to secure licensees will provide ample opportunity for Republicans and others opposed to the Administration to focus attention on this decision and on its aftermath.

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LIST OF MEMBERS INTERESTED IN THE RU-486 ISSUE

HOUSE

Ron Wyden
Henry Waxman
Michael McNulty (D-NY)
Jim Bunning (R-KY)
Robert Dornan (R-CA)
Duncan Hunter (R-CA)

SENATE

Carol Moseley Braun (D-IL)
Paul Simon (D-IL) (wrote on behalf of constituent)
John Breaux (D-LA) (wrote on behalf of constituent)

BACKGROUND

For five years Wyden has been by far the most active and vocal Member on RU-486. He has held numerous hearings and cosponsored a bill with Waxman in the last Congress to overturn the FDA import ban. Also in the last Congress, 6 Republicans (Dornan, Dannemeyer, Lent, Bartlett, Bunning, and Hunter) cosponsored a bill to prohibit federal funds from being used for clinical studies of RU-486 as an abortifacient. No one in the Senate is consistently active on this issue.

Obviously, the womens' caucus will be interested in any actions taken on Ru-486 as will the pro-life caucus (especially Hyde, Helms, and C. Smith). However, in the last four years the Department has not received RU-486 letters from either group.

Very little mail has been received by the Clinton Administration on RU-486. A typical letter is the attached C. Moseley-Braun letter inquiring as to the status of the President's Directives.

In the Bush Administration a typical letter is the attached California delegation letter on RU-486 as an important option for American women. Also, letters often stressed the importance of allowing research on RU-486 to go forward in areas of breast cancer, glaucoma, Cushing's disease, etc.

Please let me know if I can get additional information for you.

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PRESS ISSUES DISCUSSION

If negotiations with the Population Council collapse, the Clinton Administration will be left with two possible courses of action. The following is an examination of the public relations ramifications of both choices:

If the Administration decides to accept the gift of the patent from Roussel Uclaf, for purposes of insulating the White House, it should be accepted by Secretary Donna Shalala at the direction of the President of the United States and on behalf of the women in America. This could be done in a press conference on Friday, May 13, 1994, with up to four principals: Secretary Shalala, Roussel Uclaf President, Population Council (if they would agree to run the clinical trials) and possibly Congressman Ron Wyden (who has been pushing this issue on Capitol Hill).

It would be made very clear that this step is the result of the process that was set in motion by President Clinton's memorandum of January 22, 1993, and that it is being taken because it was impossible for Roussel Uclaf to come to closure with a private sector entity. Because a non-surgical (and sometimes safer) abortion alternative would thus be available to women in the United States (as it is to many women in Europe), accepting the patent gift should be touted as a reproductive rights victory for American women and another example of the Clinton Administration's commitment to deliver on its promises. However, Secretary Shalala's remarks would be tempered by caution about the long and difficult road ahead and the potential roadblocks to bringing RU 486 to the marketplace.

While it should not be a part of the formal press conference, there should be a concerted effort on the part of the HHS Public Affairs team to place stories that outline the hurdles that must be overcome to shield the Administration against the fallout from our allies in the event efforts to get RU 486 to market become stalled in bureaucratic process, in Congress or for other reasons.

Because the Clinton Administration would actually be in possession of the RU 468 patent for a period of time while the licensing process moves foreward, during that time, the Administration may well be the focus of protest by conservative organizations that have become increasingly vocal and militant. These groups have suffered recent setbacks in court (e.g. a ruling that has imposed massive fines and barred them from physically blocking access to abortion facilities). They would welcome an extremely high visibility focal point for their activities. Protest marches in front of the White House and HHS are imaginable, and the conservative talkshow circuit would help to sustain the furor. This could go on while other abortion-related issues are before Congress, including debate on the Health Security Act and the FY 1995 enactment of the Hyde

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Amendment. In the worst case, it could put the abortion issue centerstage, with the Clinton Administration as a high-profile player right up through the kick-off of the 1996 re-election campaign.

It would also be necessary to recruit a cadre of lawmakers, pro-choice and women's advocates willing and able to speak up for the Administration over the course of this heated debate. That is critically important for holding our own on the conservative talkshow circuit.

If the Administration decides to reject the gift of the patent from Roussel Uclaf, news of that decision should be disclosed in a press conference on Friday, May 13, 1994, by Secretary Shalala and FDA Commissioner David Kessler. It will be necessary to construct a rationale for why that course of action is better than the alternative one for American women. The argument will have to be that giving the patent to the United States government does not speed the drug to the American marketplace. In fact, it does just the opposite. Administrative regulatory process and the potential for legislative stonewalling could be very time consuming and could ultimately prevent the women in America from gaining access to RU 486.

We should also highlight in the Secretary's statement the unprecedented nature of what Roussel Uclaf was attempting to position the United States to do. Never before has a patent been accepted by the government. The novelty of the situation makes the issue potentially more likely to be tied up in litigation or legislative maneuvering. One of the speakers would provide details of the formidable obstacles that may delay or even prevent the United States from moving the drug onto the market.

If Roussel Uclaf is willing to grant the United States patent rights for using RU 486 only for abortifacient and other gynecological purposes, another potential argument we could embrace is the position that we wanted more than the rights they were willing to grant because our interest in this drug goes beyond the issue of abortion, the need for which we are committed to making as rare as possible.

We would stress that a private sector deal is the only viable option for getting RU 486 quickly through clinical trials and into the market place. We should outline in detail all that the Population Council did to try and close the deal during the 14-month negotiations with Roussel Uclaf. The message, either implicitly or explicitly, is that Roussel Uclaf does not really want to close a deal with an entity that clearly has the potential to bring RU 486 to the marketplace because the company fears pressure from American conservatives.

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Our position should be publicly to challenge Roussel Uclaf to go back to the bargaining table with the Population Council or to open negotiations with another entity; to stop playing games; and to get serious about responding to the request that President Clinton made of them almost a year and a half ago.

Without a doubt, a "no" will subject the Administration to a firestorm of protest by pro-choice and women's groups; and there will be few natural political allies vocally defending this decision, particularly in light of the relative difficulty of explanation.

* * * * * * *

It should be noted that Roussel Uclaf has already begun, informally, to circulate word of its potential offer to the United States. Many representatives of the pro-choice community already know about the potential gift offer. We may be forced to confront a news account of the issue prior to the Congressional hearings on May 16, 1994. Such a story will, undoubtedly, be presented from the Roussel Uclaf perspective as opposed to the Administration's point of view.

THE WHITE HOUSE
WASHINGTON

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

In Import Alert 66-47, the Food and Drug Administration ("FDA") excluded the drug Mifepristine -- commonly known as RU-486 -- from the list of drugs that individuals can import into the United States for their "personal use," although the drugs have not yet been approved for distribution by the FDA. (*See* FDA Regulatory Procedures Manual, Chapter 9-71.) Import Alert 66-47 effectively bans the importation into this Nation of a drug that is used in other nations as a nonsurgical means of abortion.

I am informed that in excluding RU-486 from the personal use importation exemption, the FDA appears to have based its decision on factors other than an assessment of the possible health and safety risks of the drug. Accordingly, I hereby direct that you promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. Furthermore, if the FDA concludes that RU-486 meets the criteria for the personal use importation exemption, I direct that you immediately take steps to rescind Import Alert 66-47.

In addition, I direct that you promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 or other antiprogestins.

You are hereby authorized and directed to publish this memorandum in the *Federal Register*.

William J Clinton

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ROUSSEL UCLAF

Professeur Ernst-Günter Afting
Président du Directoire

Paris, May 9, 1994

Honorable Donna SHALALA
Secretary of Health and Human Services
Room 615 F
Hubert Humphrey Building
200 Independence Avenue SW
WASHINGTON, D.C. 20201
USA

Attention : Mr. Kevin THURM

Dear Secretary Shalala,

Following various meetings with your Staff and with FDA officers, the latest on May 6, 1994 with Dr. Kessler, we would like to confirm that we are ready to assign our US patent rights on RU 486 in accordance with the attached draft letter from us to the President of the United States of America.

This document is substantially similar to the draft that was given to Mr. Kevin Thurm, on April 29, 1994, by our counsel Lester Hyman, to allow a review of the situation by your Administration.

Of course we will continue to work with you and all relevant people in a constructive spirit and we look forward to meet you personally by the end of this week, as planned.

Sincerely,

Pr. E-G. AFTING
President & CEO

cc. Dr. KESSLER

35, Boulevard des Invalides 75323 Paris Cedex 07
[illegible]

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ROUSSEL UCLAF

DRAFT

Paris, May ..., 1994

Honorable William J. CLINTON
President of the United States
The White House
1600 Pennsylvania Avenue NW
WASHINGTON, D.C. 20500
USA

Attention : Ms. Nancy HERNREICH

Dear Mr. President,

You have requested that ROUSSEL UCLAF allow the RU 486 compound to be used in your country.

We have been working to react to that request in a responsible manner.

I now am pleased to inform you that we have decided to contribute mifepristone (RU 486) for abortifacient purposes (and other gynecological uses) to the people of the United States of America, completely free of charge, by voluntarily assigning our relevant patent rights to the US Government.

This an unconditional gift, we ask for nothing in return.

Sincerely,

Pr. E-G. AFTING
President & CEO

35, Boulevard des Invalides 75323 Paris Cedex 07

PROJET 09.05.94

ROUSSEL UCLAF
Société anonyme à Directoire et Conseil de Surveillance
au capital de 544.749.380 F.
Siège social : 35, Boulevard des Invalides 75007 PARIS
R.C.S. Paris B 542 [illegible]

Extrait du Projet de Procès-Verbal
de la séance du Conseil de Surveillance du 4 Mai 1994
à 17 h 30

Présents

Membres du Conseil de Surveillance :

Dr. E. SAKIZ, Président,
Dr. M. FRUEHAUF, Vice-Président,
MM. J. BOISSON, C. de CROISSET, le Pr. J. DAUSSET, B. ESAMBERT,
le Pr. G. MILHAUD, H. MONOD, E. de ROYERE, le Dr. K.G. SEIFERT.

Sans voix délibérative :

Pr. E.G. AFTING, Président du Directoire,
M. G. JACQUESSON, Directeur Général, Membre du Directoire,
M. D. CAMUS, Membre du Directoire,
M. B. WINICKI, Membre du Directoire.

M. J.F. CHAVANCE et Mme D. PIERRON, Délégués du Comité Central d'Entreprise.

M. F. DESCOURS, Secrétaire du Conseil.

Absents excusés

M. le Dr. G. METZ, Membre du Conseil de Surveillance,
M. J. MISCHE, Membre du Conseil de Surveillance.
MM. P. BRECHARD et D. GAILLET, Délégués du Comité Central d'Entreprise.

……

.../...

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PROJET 09.05.94

2.

MIFÉPRISTONE - ÉTATS-UNIS

Le Docteur E. SAKIZ informe le Conseil de Surveillance que son assentiment est demandé sur les décisions que le Directoire va être amené à prendre à propos de la mifépristone aux États-Unis d'Amérique, compte tenu des exigences pressantes formulées au plus haut niveau par les autorités gouvernementales fédérales de ce pays.

Étant donné les caractères très particuliers du système médical des États-Unis par comparaison à celui des pays d'Europe où la mifépristone est actuellement utilisée, et considérant également le climat hautement conflictuel créé autour de ce produit aux États-Unis, le Directoire estime que ROUSSEL UCLAF ne saurait en aucune façon s'impliquer elle-même dans la production ou la diffusion de la mifépristone aux États-Unis.

Toutefois, prenant acte de la volonté du gouvernement américain de procurer aux citoyennes des États-Unis cette alternative médicale à l'interruption chirurgicale de la grossesse, le Directoire s'est résolu à offrir au gouvernement des États-Unis de lui céder, sans rémunération, les deux brevets référencés "U.S. Patents Nos. 4,386,085 and 4,447,424".

Au cas où ce gouvernement déclinerait cette offre pour lui-même tout en la jugeant recevable par une institution qu'il désignerait à cet effet, ROUSSEL UCLAF accepterait de poursuivre dans cette voie et de passer les accords nécessaires, à condition d'en être formellement requise par une lettre officielle, portant la signature du Président des États-Unis, et d'obtenir un certain nombre de garanties contractuelles.

Le Conseil de Surveillance prend acte de cette position qui n'appelle de sa part aucune objection, et manifeste ainsi au Directoire l'assentiment de principe sollicité.

……

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[Translation of Fax from Dr. Sakiz to Mary Pendergast of draft minutes of the Supervisory Board Meeting of May 4, 1994]

MIFEPRISTONE - UNITED STATES

Dr. E. SAKIZ informed the Supervisory Board ("Conseil de Surveillance") that its assent is requested concerning decisions that the Director ["le Directoire"] is being led to take a propos mifepristone in the United States of America, taking account of pressing exigencies formulated at the highest level by authorities of the federal government of that nation.

Given the very particular characteristics of the U.S. medical system, in comparison to that of the European countries where mifepristone is currently used, and considering equally the highly conflicted climate created around this product in the U.S., the Director deems that ROUSSEL UCLAF would be in no way implicated itself in the production or distribution of mifepristone in the United States.

Nevertheless, considering the wish of the American government to procure for U.S. citizens this medical alternative to the surgical termination of pregnancy, the Director has resolved to offer to cede to the government of the United States, without remuneration, the two patents referred to as "U.S. Patents Nos. 4,386,085 and 4,447,424."

In the event that the government should decline this offer for itself and at the same time judging it receivable by an institution that it would designate to this end, ROUSSEL UCLAF would accept this path and would adopt the necessary agreements, on the condition of being formally required by an official letter, bearing the signature of the President of the United States, and of obtaining a certain number of contractual guarantees.

The Supervisory Council acknowledged this position, which generated no objections, and manifested to the Director its assent to the principle being offered.

[translated by L. Bachorik, 5/10/94]

Tab E

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THE WHITE HOUSE
WASHINGTON

May 16, 1994

Dr. Edouard Sakiz
Chairman, Supervisory Board
Roussel Uclaf
35, boulevard des Invalides
75323 Paris Cedex 07
FRANCE

file

Dear Dr. Sakiz:

It is important for the health of women in the United States that they have access to the widest possible range of safe and effective medical treatments. In support of that goal, in January 1993, I asked the Secretary of Health and Human Services to promote the testing and licensing of mifepristone (RU 486) and other antiprogestins in the United States.

I understand that since at least that time, your company has been in negotiations with The Population Council, Inc., a nonprofit organization with whom you have had dealings on mifepristone since early in the last decade. Those discussions, I understand, have been directed toward the purpose on which I charged the Secretary. I am grateful for the effort those negotiations represent.

In order to permit the appropriate testing, development, and distribution of your product, I urge, at the conclusion of your negotiations, that you bring your plans to fruition. I understand that your company will assign without remuneration your United States patent rights on mifepristone to The Population Council, Inc. which has been studying this product since 1982 and which would take all necessary steps to file a new drug application with the Food and Drug Administration, so that the agency can determine whether the drug is safe and effective for use in the United States.

On behalf of the government of the United States and for the women in America, I thank you for your work.

Sincerely,

Bill Clinton

Tab F

Clinton Library Photocopy

BETSEY WRIGHT

cc for ~~Shalala~~ on Tues

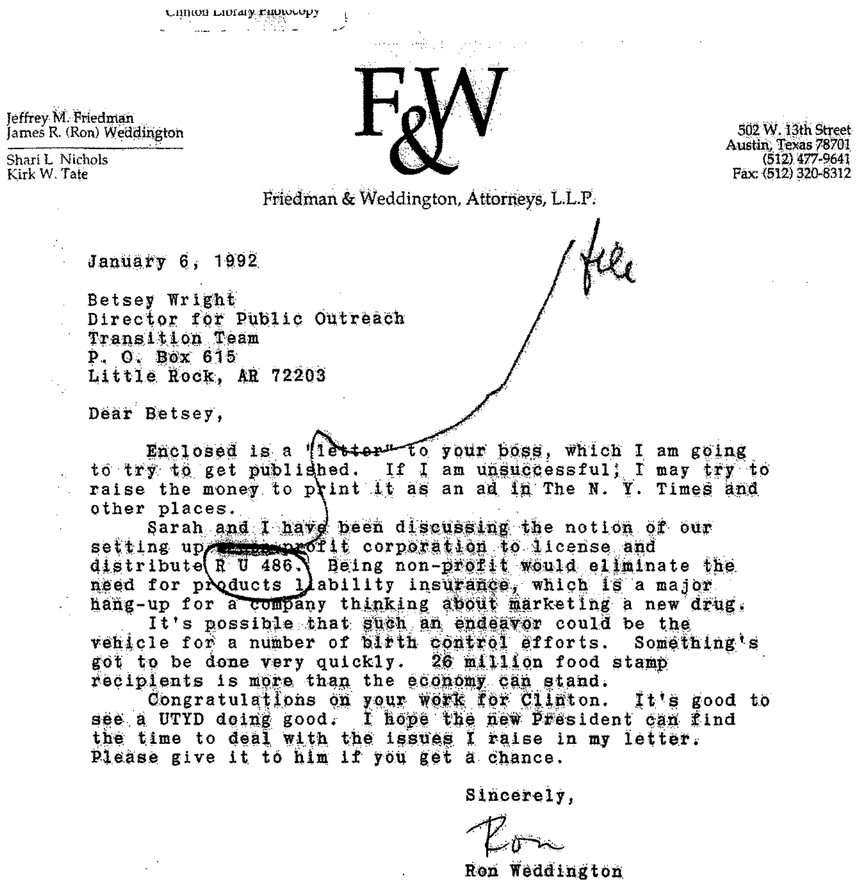
To Randa

pk

To Carol Rasco

This just got forwarded to me please handle

BW
3/9/93



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F&W

Jeffrey M. Friedman
James R. (Ron) Weddington

Shari L. Nichols
Kirk W. Tate

Friedman & Weddington, Attorneys, L.L.P.

502 W. 13th Street
Austin, Texas 78701
(512) 477-9641
Fax: (512) 320-8312

file

January 6, 1992

Betsey Wright
Director for Public Outreach
Transition Team
P. O. Box 615
Little Rock, AR 72203

Dear Betsey,

Enclosed is a "letter" to your boss, which I am going to try to get published. If I am unsuccessful, I may try to raise the money to print it as an ad in The N. Y. Times and other places.

Sarah and I have been discussing the notion of our setting up [illegible]profit corporation to license and distribute R U 486. Being non-profit would eliminate the need for products liability insurance, which is a major hang-up for a company thinking about marketing a new drug.

It's possible that such an endeavor could be the vehicle for a number of birth control efforts. Something's got to be done very quickly. 26 million food stamp recipients is more than the economy can stand.

Congratulations on your work for Clinton. It's good to see a UTYD doing good. I hope the new President can find the time to deal with the issues I raise in my letter. Please give it to him if you get a chance.

Sincerely,

Ron

Ron Weddington

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Jeffrey M. Friedman
James R (Ron) Weddington
Shari L. Nichols
Kirk W. Tate

F&W
Friedman & Weddington, Attorneys, L.L.P.

502 W. 13th Street
Austin, Texas 78701
(512) 477-9641
Fax: (512) 320-8312

Dear President-To-Be Clinton,

Some years ago another Southern Governor, when asked about the possibilities for prison reform, supposedly said something to the effect of, "Well, I don't think we're going to get very far until we get a better class of prisoner."

Well, I don't think you are going to get very far in reforming the country until we have a better educated, healthier, wealthier population.

Face it, you know that anything that even resembles the programs of Democratic Presidents in the past is going to make you a one term President. Reagan spent all our money on bombs and even if there were money for programs such as pre-natal health care, job training and day care centers it would be years before we would see any dramatic results. And, as anyone who follows education can see, more money doesn't necessarily translate into better educated kids.

But you can start immediately to eliminate the barely educated, unhealthy and poor segment of our country. No, I'm not advocating some sort of mass extinction of these unfortunate people. Crime, drugs and disease are already doing that. The problem is that their numbers are not only replaced but increased by the birth of millions of babies to people who can't afford to have babies.

There, I've said it. It's what we all know is true, but we only whisper it, because as liberals who believe in individual rights, we view any program which might treat the disadvantaged differently as discriminatory, mean-spirited and...well...so Republican.

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In 1989, 27 percent of all births were to unmarried mothers, a huge percentage of whom were teenagers. If current trends continue, soon a majority of the babies born will be born into poverty and one half of the country cannot support the other half, no matter how good our intentions.

I am not proposing that you send federal agents armed with Depo-Provera dart guns to the ghetto. You should use persuasion rather than coercion. You and Hillary are a perfect example. Could either of you have gone to law school and achieved anything close to what you have if you had three or four or more children before you were 20? No! You waited until you were established and in your 30's to have one child. That is what sensible people do. For every Jesse Jackson who has fought his way out of the poverty of a large family there are millions mired in poverty, drugs and crime.

If Ronald Reagan could use the media to convince the American public that a trillion dollars of borrowed money needed to be spent to combat the "Evil Empire," then you ought to be able to persuade people to only have children when they are able to afford them. Point out that only people like George Bush who inherit money can pay for more than one or two kids in today's economy. (And even then, some of the kids grow up to do embarassing things like loot savings and loans.)

You made a good start when you appointed Dr. Elders, but she will need a lot of help. You will have to enlist the aid of sports and entertainment stars to counteract the propaganda spread by church officials seeking parishioners, generals seeking cannon fodder and businessmen seeking cheap labor that, throughout the ages, has convinced the poor that children are necessary to fulfillment as a person.

It wouldn't hurt to point out that while only 11.1 percent of three person families are below the poverty level, 20.2 percent of six person families and 28.6 percent of families of seven or more are poor. (1992 Statistical Abstract of the United States, p. 459)

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And, having convinced the poor that they can't get out of poverty when they have all those extra mouths to feed, you will have to provide the means to prevent the extra mouths, because abstinence doesn't work. The religious right has had 12 years to preach their message. It's time to officially recognize that people are going to have sex and what we need to do as a nation is prevent as much disease and as many poor babies as possible.

Condoms alone won't do it. Depo-Provera, Norplant and the new birth control injection being developed in India are not a complete answer, although the savings that could be effected by widespread government distribution and encouragement of birth control would amount to billions of dollars.

No, government is also going to have to provide vasectomies, tubal ligations and abortions...RU 486 and conventional abortions. Even if we make birth control as ubiquitous as sneakers and junk food, there will still be unplanned pregnancies. There have been about 30 million abortions in this country since Roe v. Wade. Think of all the poverty, crime and misery ...and then add 30 million unwanted babies to the scenario. We lost a lot of ground during the Reagan-Bush religious orgy. We don't have a lot of time left.

You could do it, Mr. President-To-Be. You are articulate and you've already alienated the religious right with your positions on abortion and homosexuals. The middle-class taxpayer will go along with this plan because it will mean fewer dollars for welfare. The retirees will also go along because because poor people contribute very little to Social Security.

And the poor? Well, maybe if we didn't have to spend so much on problems like low birth weight babies and trying to educate children who come to school hungry, we might have some money to help lift the ones already born, out of their plight.

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The biblical exhortation to "Be fruitful and multiply," was directed toward a small tribe, surrounded by enemies. We are long past that. Our survival depends upon our developing a population where everyone contributes. We don't need more cannon fodder. We don't need more parishioners. We don't need more cheap labor. We don't need more poor babies

Very truly yours,

Ron Weddington

P.S. I was co-counsel in Roe V. Wade, have sired zero children and one fetus, the abortion of which was recently recounted by my ex-wife in her book, A Question Of Choice. (Grosset/Putnam, 1992) I had a vasectomy in 1969 and have never had one moment of regret.

Mr. SOUDER. RU–486 was forced through the FDA using an extraordinary provision called Subpart H, reserved only for drugs that treat life-threatening illnesses and for which existing treatments are insufficient. It was obvious even to the drug's sponsor that RU–486 did not fall within the narrow scope of Subpart H, saying the FDA's imposition of Subpart H was unlawful, unnecessary, and undesirable. But that did not deter the FDA in its extraordinary political complicity with President Clinton's administration from forcing an abortion pill onto the market, no matter how distorted the approval process was or what the price.

We are paying that price now. Almost 1,000 women have suffered adverse effects after taking RU–486. We know that eight have died. We have a responsibility to consider the dangers that this drug poses and question whether the FDA has the authority to remove it from the market in the light of the severe problems associated with this drug and the manufacturer's failure to comply with post-marketing restrictions.

I anticipate that the defenders of RU–486 will try to detract from the cold, hard facts or cause confusion by talking about other septic infections in other pregnancy situations. This tactic ignores what the panelists reported at last week's CDC conference, that Mifeprex compromises the innate immune system, providing an environment for rapid growth of the deadly infection.

C. Sordellii infection in the RU–486 context is 100 percent fatal, with no opportunity for intervention. To ignore the immune system connection with Mifeprex, or to say that there have been only five such deaths and advocate only for better surveillance and informed consent will be no comfort to the family of the next women who dies suddenly after taking RU–486.

To the shallow objection that those of us who are pro-life have no business looking into the problems associated with RU–486, let me respond that this is a smokescreen and is incredibly shameful. Anyone who honestly cares about women's health has to take a critical look at the potential dangers of this drug. To argue otherwise, on the basis that it is simply an abortion issue, is to demonstrate a blind allegiance to abortion at any cost, including women's lives.

Representing the FDA on the first panel is Dr. Janet Woodcock, Deputy Commissioner for Operations.

On our second panel, we will hear from Monty Patterson, the father of Holly Patterson, who was 18 years old when she died after taking RU–486; Dr. Susan Wood, former FDA Assistant Commissioner for Women's Health; Dr. Lisa Rarick of RAR Consulting; Dr. Donna Harrison, a member of the Mifeprex Subcommittee of the American Association of Prolife Obstetricians and Gynecologists, and Carter Snead, Associate Professor of Law at Notre Dame and former General Counsel for the President's Council on Bioethics.

I wish to note that the medical director for Danco, the Cayman Islands-based manufacturer for RU–486, initially agreed to testify at this hearing, but pulled out 2 days ago. I intend to followup with Danco to request answers in a sworn affidavit to critical questions regarding Danco's failure to comply with the post-marketing restrictions for RU–486.

Last of all, I want to note that I notified the FDA last December that this subcommittee would conduct a hearing into RU–486. FDA's compliance with this oversight committee's document requests has been quite frustrating. We were getting critical documents related to our December request as late as last night. This hearing is not the end of our document requests and I invite better cooperation from the agency moving forward. Now that we are here and we have most of the documents we requested 5 months ago, it is time to seek some answers about what can be done to protect women from this deadly drug.

[The prepared statement of Hon. Mark E. Souder follows:]

Subcommittee on Criminal Justice, Drug Policy and Human Resources

Opening Statement of Chairman Mark Souder

"RU-486: Demonstrating a Low Standard for Women's Health?"

May 17, 2006

We are here today because there is a drug on the market associated with the deaths of at least eight women, nine life-life threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection.[1] There have been more than 950 adverse event cases associated with RU-486, out of only 575,000 prescriptions[2] *at most.* Adverse events are typically underreported, since they are offered voluntarily by consumers and health care professionals, so it is most likely there are many more cases that we don't even know about.

It's very clear that there is a serious problem with RU-486, and failing to address this problem by disguising it, ignoring it, minimizing it or causing confusion is a shameful failure for anyone with the ability and desire to protect women from needless harm.

RU-486 is the common name for Mifeprex. It is produced by Danco Laboratories, a corporate entity located in the Cayman Islands which produces only that single drug, and nothing else. Mifeprex is approved by the FDA for the termination of pregnancy through 49 days of development. It is used in combination with another drug called misoprostol, which causes uterine contractions that expel the dead fetus. This is an off-label use for misoprostol, which contains a black-box warning against using the drug during pregnancy.

At least five of the deaths following the use of RU-486 have been the result of a toxic shock-like syndrome initiated by the bacteria Clostridium Soredellii. This bacteria is thought to exist in low numbers in the reproductive tracts of many women, and is normally combated by the immune system. Experts in immunology,[3] pharmacology,[4] and maternal-fetal medicine[5] have suggested that because RU-486 interferes with the innate immune response, the bacteria, if present, is allowed to flourish, causing a widespread, multi-organ infection in the woman.

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[1] Letter from David W. Boyer, Assistant Commissioner for Legislation, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 2, 2006) (on file with Subcommittee).

[2] *Id.*

[3] *See,* Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in...mifepristone...enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486.")

These infections are not accompanied by a fever, and the symptoms match those that are expected after taking the RU-486 regimen, including cramping, pain, bleeding, nausea, vomiting. Each of the women infected with C. Sordellii after taking RU-486 were dead within five to seven days.

To investigate the nature of this bacteria, the CDC and FDA held a scientific workshop last week called "Emerging Clostridial Disease." The workshop panelists noted that the rapid growth of the C. Sordellii bacteria in the RU-486 context likely forecloses effective treatment, and that there is no currently identifiable "window of opportunity" for treatment once a woman is infected, even with major interventions such as hysterectomy. The fatality rate has been 100% for the women who contracted C. Sordellii infection after RU-486.

Any other drug associated with a 100% fatal septic infection that kills otherwise healthy adults within days, with no apparent window for treatment, and associated with an exponential amount of severe reactions, would normally prompt an immediate withdrawal.

But we are talking about a drug regimen that is administered to cause an abortion, manufactured by a drug company based in the Caymen Islands, with no other drugs on the market, and therefore no incentive to voluntarily withdraw its product, no matter how dangerous. Many abortion advocates feel they have to defend this RU-486 because it is an alternative to surgical abortion. However, with eight deaths that we know about, RU-486 is ten to fourteen times more likely to be fatal than surgical abortion during the first seven weeks of pregnancy, the period during which the drug is administered.[6]

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[4] *See,* Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors...results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The combined loss of a closed cervix and the protective cervical mucus plug permits contamination of the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

[5] *See,* Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.")

[6] The mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available for women. Dr. Michael Green of Harvard based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. *See,* Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318. Current numbers suggest, however, eight deaths in the United States, while, according to the manufacturer, 575,000 women have used the drug. This works out to 1 in about 71,875, or 1.39 for every 100,000.

To continue defend this dangerous drug in light of mounting scientific evidence, injury and death is to allow one's zeal for abortion to truly distort their view about what's right for women's health. The ten-times-more-deadly danger posed by RU-486 should not be considered an "acceptable risk" that justifies keeping this drug on the market.

The approval of RU-486 was made under extreme political pressure from the Clinton Administration, which is well-documented in a recent report by Judicial Watch entitled "The Clinton RU-486 Files."[7] I ask that this report be included in the hearing record.

RU-486 was forced through the FDA using an extraordinary provision called "Subpart H," reserved only for drugs that treat life threatening illnesses, and for which existing treatments are insufficient.[8] It was obvious even to the drug sponsor that RU-486 did not fall within the narrow scope of Subpart H, saying that FDA's imposition of Subpart H was "unlawful, unnecessary, and undesirable."[9] But that did not deter the FDA in its extraordinary political complicity with President Clinton's Administration from forcing an abortion pill onto the market, no matter how distorted the approval process was, or what the price.

We are paying that price right now. Almost one thousand women have suffered adverse events after taking RU-486. We know that eight that have died. We have a responsibility to consider the dangers that this drug poses, and question whether FDA has the authority to remove it from the market in light of the severe problems associated with this drug and the manufacturer's failure to comply with post-marketing restrictions.

I anticipate that defenders of RU-486 will try to detract from the cold, hard facts, or cause confusion, by talking about other septic infections in other pregnancy situations. This tactic ignores what panelists reported at last week's CDC conference: that *Mifeprex compromises the innate immune system, providing an environment for rapid growth of the deadly infection.*

C. Sordellii infection in the RU-486 context is 100% fatal, with no opportunity for intervention. To ignore the immune system connection with Mifeprex, or to say that there have been "only five" such deaths, and advocate only for better surveillance and informed consent, will be no comfort to the family of the next woman who dies suddenly after taking RU-486.

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[7] A Judicial Watch Special Report: The Clinton RU-486 Files, The Clinton Administration's Radical Drive to Force an Abortion Drug on America, April 26, 2006. Available at http://judicialwatch.org/archive/2006/jw-ru486-report.pdf (last visited May 17, 2006).

[8] 21 CFR 314.500 (1999).

[9] Letter to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products, from Sandra Arnold, Vice President, Corporate Affairs of the Population Council, (Sept. 6, 2000) [Cited in Citizen Petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days' Gestation, (Aug. 21, 2002), on file with the subcommittee].

To the shallow objection that those of us who are pro-life have no business looking into the problems associated with RU-486, let me respond: that is a smokescreen, and it is incredibly shameful. Anyone who honestly cares about women's health has got to take a critical look at the potential dangers of this drug. To argue otherwise, on the basis that this is simply an "abortion" issue, is to demonstrate a blind allegiance to abortion at any cost, including women's lives.

Representing the FDA on the first panel is Dr. Janet Woodcock, Deputy Commissioner for Operations. On our second panel, we'll hear from Monty Patterson, the father of Holly Patterson, who was 18 years old when she died after taking RU-486; Dr. Susan Wood, Former FDA Asst. Commissioner for Women's Health; Dr. Lisa D. Rarick, of RAR Consulting; Dr. Donna Harrison, a Member of the Mifeprex Subcommittee of the American Association of Prolife Obstetricians and Gynecologists; and Carter Snead, Associate Professor of Law at the University of Notre Dame, and former General Counsel for the President's Council on Bioethics.

I wish to note that the Medical Director for Danco, the Cayman Islands-based manufacturer of RU-486, initially agreed to testify at this hearing, but pulled out two days ago. I intend to follow up with Danco to request answers in a sworn affidavit to critical questions regarding Danco's failure to comply with post-marketing restrictions for RU-486.

Last of all, I want to note that I notified the FDA last December that this Subcommittee would conduct a hearing into RU-486. [10] FDA's compliance with this oversight committee's document requests has been quite frustrating; we were getting critical documents related to our December request as late as last night. This hearing is not the end of our document requests, and I invite better cooperation from the agency moving forward. Now that we are here, and that we have most of the documents we requested five months ago, it's time to seek some answers about what can be done to protect women from this deadly drug.

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[10] Letter from Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, to Hon. Andrew von Eschenbach, M.D. (Dec. 21, 2005), at http://reform.house.gov/CJDPHR/News/DocumentSingle.aspx?DocumentID=38547.

Mr. SOUDER. Now I yield to the ranking member, Mr. Cummings, for his opening statement.

Mr. CUMMINGS. Thank you very much, Mr. Chairman. I want to join you in welcoming all of our witnesses testifying this afternoon on a very important subject, protecting women's health.

And particularly, I want to acknowledge Mr. Monty Patterson, who lost his 18-year-old daughter, Holly, when she died as a result of a rare bacterial infection. I offer my sincere condolences to the Patterson family and want to commend Mr. Patterson and his family for their efforts to become well-versed in this subject area in the wake of a terrible family tragedy.

As you know, Mr. Chairman, C. Sordellii is a bacterium that normally resides in soil. Although cases of human illness are rare, the effect is usually fatal when the bacteria produces toxins that cause rapid onset of shock that physicians are powerless to curtail.

To date, medical literature reflects a total of approximately 30 reported fatalities from C. Sordellii infection. Cases of infection have involved both males and females of all ages. At least eight of the reported fatalities occurred in women who had just given birth, and two occurred after miscarriages.

The selective focus of today's hearing centers on five fatal cases that have occurred over the past 5 years and also involved pregnancy. Four of these cases occurred in California, the other in Canada. The key factor linking this small subset of cases is that they occurred in women who underwent medical abortion.

Last week, the Centers for Disease Control, as you said, convened a scientific meeting on C. Sordellii and another related bacterium. The meeting served to underscore just how little is known about the cause of human C. Sordellii infections. Although a number of theories were advanced and debated, the meeting produced no solid answers as to how the infection is acquired. The only consensus was that much more needs to be learned if additional deaths are to be prevented.

Despite the overwhelming scientific uncertainty among experts, a number of policymakers and policy shapers apparently have already arrived at the conclusion that the drug Mifepristone, also known as RU–486 and marketed in the United States under the name Mifeprex, is the likely cause of the infection in the five cases involving patients who underwent medical abortion. Consequently, they are advocating the FDA's immediate withdrawal of Mifeprex from the market. What is the basis for this belief? Is it science, or is it something else?

It is difficult to overlook the fact that adherents to this point of view generally opposed the introduction of Mifepristone into the United States in the first place, or to ignore the fact that they did so on an ideological grounds, knowing that there had been no reported fatalities among as many as 2 million users of the drug in Europe.

To bolster their argument, proponents of withdrawing FDA approval suggest that the FDA, in effect, rushed the drug to market. But the record shows that the approval process was thorough and unusually lengthy. However, it resulted in more stringent restrictions on distribution than apply to most other drugs.

Mr. Chairman, I hope it is fair and correct to presume that not one participant in today's hearing takes the health of women lightly. As a matter of fact, every single one of us take women's health very seriously. My own concern for both women's health and women's rights leads me to wonder, however, why the narrow focus on these cases and on this drug as the suspected culprit? Why not concern ourselves with all the possible causes of infection in not only these 5 cases, but also the other 9 or 10 reported cases in which pregnancy was the common denominator?

If ensuring a high standard of health care for American women is our pure objective, it just seems to me, Mr. Chairman, that our focus should be seeking the truth concerning the cause of C. Sordellii infection rather than attempting to bully the FDA into taking action, unsupported by science, that would have just one certain impact, limiting access to abortion for many, many women.

Therefore, I hope today's hearing can serve the purpose of promoting thorough scientific inquiry and supporting a research agenda that will lead us to answers that can prevent infection and death from infection.

Concentrating on five cases involving medical abortion to the exclusion of a larger number of equally tragic cases appears to serve the narrow purpose of whittling away at a women's constitutional right to choose by limiting practical access to abortion. I only hope that, in this case, appearances are deceiving.

I look forward to the testimony and I thank the witnesses for being with us, and with that, Mr. Chairman, I yield back.

[The prepared statement of Hon. Elijah E. Cummings follows:]

Rep. Elijah E. Cummings, D-MD7
Ranking Minority Member
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
U.S. House of Representatives
109th Congress

Hearing on "RU-486: A Low Standard for Women's Health?"

May 17, 2006

Mr. Chairman,

I want to join you in welcoming all of our witnesses testifying this afternoon on a very important subject: protecting women's health.

In particular, I want to acknowledge Mr. Monty Patterson who lost his 18-year-old daughter, Holly, when she died as the result of a rare bacterial infection. I offer my sincere condolences to the Patterson family and want to commend Mr. Patterson for his efforts to become well-versed in this subject area in the wake of a terrible family tragedy.

As you know, Mr. Chairman, *C. Sordellii* ("Cee sore-DELL-ee-eye") is a bacterium that normally resides in soil. Although cases of human illness are rare, the effect is usually fatal when the bacteria produce toxins that cause rapid onset of shock that physicians are powerless to curtail.

To date, the medical literature reflects a total of approximately 30 reported fatalities from *C. sordellii* infection. Cases of infection have involved both males and females of all ages.

At least eight of the reported fatalities occurred in women who had just given birth, and two occurred after miscarriages.

The selective focus of today's hearing centers on five fatal cases that have occurred over the past five years and also involved pregnancy. Four of these cases occurred in California, the other in Canada. The key factor linking this small subset of cases is that they occurred in women who underwent medical abortion.

Last week, the Centers for Disease Control convened a scientific meeting on *C. sordellii* and another, related bacterium. The meeting served to underscore just how little is known about the cause of human *C. sordellii* infections. Although a number of theories were advanced and debated, the meeting produced no solid answers as to how the infection is acquired. The only consensus was that much more needs to be learned if additional deaths are to be prevented.

Despite the overwhelming scientific uncertainty among experts, a number of policy makers and policy shapers apparently have already arrived at the conclusion that the drug mifepristone ("miff-eh-PRISS-tone") -- also known as "RU-486" and marketed in the United States under the name Mifeprex ("MIFF-eh-prex") – is the likely cause of the infection in the five cases involving patients who underwent medical abortion. Consequently, they are advocating the FDA's immediate withdrawal of Mifeprex from the market.

What is the basis for this belief? Is it science? Or is it something else?

It is difficult to overlook the fact that adherents to this point of view generally opposed the introduction of mifespristone into the United States in the first place -- or to ignore the fact that they did so on ideological grounds, knowing that there had been no reported fatalities among as many as 2 million users of the drug in Europe.

To bolster their argument, proponents of withdrawing FDA approval suggest that the FDA in effect rushed the drug to market; but the record shows that the approval process was thorough and unusually lengthy. Moreover, it resulted in more stringent restrictions on distribution than apply to most other drugs.

Mr. Chairman, I hope it is fair and correct to presume that not one participant in today's hearing takes the health of women lightly. My own concern for both women's health and women's rights leads me to wonder, however: why the narrow focus on these cases, and on this drug as the suspected culprit? Why not concern ourselves with all of the possible causes of infection in not only these five cases, but also the other nine or ten reported cases in which pregnancy was the common denominator?

If ensuring a high standard of health care for American women is our pure objective, it just seems to me, Mr. Chairman, that our focus should be seeking the truth concerning the cause of *C. sordellii* infection, rather than attempting to bully the FDA into taking action, unsupported by science, that would have just one certain impact: limiting access to abortion for many, many women.

Therefore, I hope today's hearing can serve the purpose of promoting *thorough* scientific inquiry and supporting a *research agenda* that will lead us to answers that can prevent infection and death from infection.

Concentrating on five cases involving medical abortion, to the exclusion of a larger number of equally tragic cases, appears to serve the narrower purpose of whittling away at a woman's constitutional right to choose, by limiting practical access to abortion. I only hope that, in this case, appearances are deceiving.

I look forward to the testimony of our witnesses and yield back my remaining time.

##

Mr. SOUDER. I now yield to other Members wishing to make opening statements. Mr. Waxman, do you have an opening statement? I am going to ask for this process. It has been a practice if Members are members of the full committee but not the subcommittee, that we let them participate, and I ask unanimous consent that Mr. Shays be allowed to participate, and he will go to the back of the rest of everybody else's opening statements.

I yield to Mr. Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman. I appreciate this chance to make an opening statement and to attend this hearing because this is an important hearing. It gives us a chance to talk about the deaths of several women who had taken Mifepristone, RU–486—we all have been stumbling over that word—which is the medical abortion pill. These deaths were tragic and I also want to join in extending my deepest sympathies to the Patterson family, who lost their daughter, and thank you for coming today.

We are going to discuss these cases as part of a broader pattern of C. Sordellii infection. This is an infection that has killed men, women, and children. It has killed women who have just given birth, women who had miscarriages, and women who had not even been pregnant. As with any infection we do not yet understand well, we need better research and surveillance to fight it.

But before we begin this discussion, I would like to say something about another reason I believe we are here. There are people who have wanted RU–486 to be pulled off the market since the day it was approved. In fact, they didn't want it to be approved. I respect their judgment because they are very strongly against an abortion, whether it be by RU–486 or by a medical procedure.

But that is not the issue of safety and it is not an issue of science and it is not an issue of data. That makes it an ideological opposition to a woman's right to choose abortion. And, in fact, many of those who want to take this drug off the market want women to have virtually zero access to any kind of abortion, whether it be medical or surgical.

I need not remind people what happened before abortion became legal and safe in the United States. Hundreds of thousands of women per year sought out illegal abortions or tried to induce abortions themselves. Tens of thousands suffered major infections and other injuries. And even after the introduction of antibiotics, hundreds of women died every year before abortion was made legal and safe.

There are many who want us to have States' rights to pass the kind of law that was just adopted in South Dakota, to ban all abortions, even in the case of rape or incest, or even to preserve the health and well-being of the mother. That is the ultimate expression of their point of view, but it is not the point of view I share and it is not the point of view that I think most people would share.

This drug, which is the subject of today's hearing, has some promising characteristics. It offers women an alternative to surgery for early termination of pregnancy. It is available to many women who do not have access to surgical abortions. And it has been widely and safely used in Europe.

On the other hand, questions have been raised about whether there may be a link between the drug and the tragic deaths of several young women. That is the question. Is there a link between this drug and those deaths? And that is a scientific issue, not an ideological one, and it is an issue that we ought to leave to the Food and Drug Administration scientists to look at the evidence.

Now, it has been asserted by the chairman that the side effects may be understated because there is voluntary disclosure. Well, that is true of all drugs—there is voluntary disclosure of adverse effects—but not this drug, because the drug had a lengthy period of time during which it was under surveillance at the Food and Drug Administration. It was approved ultimately under Subpart H, which put a lot of restrictions in place on the use of this drug which are not in place for the use of other drugs that are available on the market today in the United States. And one of the limits to its use was that a physician had to agree in advance to report any adverse consequences from use of this drug to the manufacturer and the manufacturer is obligated under law to report it to the FDA. So we have a pretty clear picture of what has been going on.

This is not like the Plan B drug, which has not been approved by the FDA for over-the-counter use because of political pressure on the FDA. This drug was not approved by political pressure, it was approved under the usual standards of safety and efficacy.

Now, other drugs have been approved under that status and have been taken off when we saw that there were consequences to it which changed the balance of whether it was a safe and efficacious drug, and that is the issue of whether this drug should remain available to women. It should be resolved based on scientific assessment of its benefits and dangers. If the best scientific evidence turns out to demonstrate that the risks do, in fact, outweigh the benefits, then the FDA should make a decision accordingly. But it should be kept on the market or removed using the same legal and scientific standards that are used for all other drugs.

For today, let us take a close and serious look at C. Sordellii infection. We must encourage our scientists to figure out why these women and the other victims of this bacteria, which had no relationship that we know of to RU–486, why they died, and we should do everything we can to improve detection and treatment. But in the end, we need to make sure any regulatory decision about RU–486 is based on the science and the law and not the politics of the abortion debate.

Thank you, Mr. Chairman.

[The prepared statement of Hon. Henry A. Waxman follows:]

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Statement of Rep. Henry A. Waxman, Ranking Minority Member
Committee on Government Reform
Statement for Hearing on
"RU-486: Setting a Low Standard for Women's Health?"

May 17, 2006

This hearing was convened so that we could talk about the deaths of several women who had taken mifepristone, the medical abortion pill.

These deaths were tragic, and I extend my deepest sympathies to the families, including Mr. Patterson, who lost his daughter. I thank him for coming today to share his experience and concerns.

We are going to discuss these cases as part of a broader pattern of C. Sordellii ["Cee sore-dell-ee-eye"] infection. This infection has killed men, women, and children. It has killed women who had just given birth, women who had miscarriages, and a woman who hadn't been pregnant. As with any infection we do not yet understand well, we need better research and surveillance to fight this.

But before we begin this discussion I would like to say something about another reason we are here.

There are people, including some in this room, who have wanted mifepristone to be pulled off the market since the day it was approved.

Well before the recent cluster of deaths, they opposed the availability of medical abortion. It had nothing to do with safety. It wasn't based on data. It was because of an ideological opposition to women's right to choose abortion.

In fact, many of those who want this drug off the market want women to have virtually zero access to any kind of abortion – medical or surgical.

So I'd like to take a moment to remind everyone of how things were before abortion became legal – and safe – in the United States.

Hundreds of thousands of women per year sought out illegal abortions, or tried to induce abortion themselves.

Tens of thousands suffered major infections and other injuries.

And even after the introduction of antibiotics, hundreds of women died every year before abortion was made legal and safe.

There are many who want every state to have a law like the new South Dakota law, which ban all abortions, even in the case of rape or incest, or to preserve the health of the mother. That is the ultimate expression of a low standard for women's health.

Mifepristone – the subject of today's hearing – has several promising characteristics. It offers women an alternative to surgery for early termination of pregnancy. It is available to many women who do not have access to surgical abortion. And it has been widely and safely used in Europe.

On the other hand, questions have been raised about whether there may be a link between the drug and the tragic deaths of several young women.

The issue of whether mifepristone should remain available to women should be resolved based on a scientific assessment of its benefits and dangers.

If the best scientific evidence turns out to demonstrate that the risks do in fact outweigh the benefits, then FDA should make a decision accordingly. But it should be kept on the market – or removed – using the same legal and scientific standards that are used for all other drugs.

For today, let's take a close and serious look at *C. sordellii* infection. We must encourage our scientists to figure out why these women and the other victims of the bacteria died. And we should do everything we can to improve detection and treatment.

But in the end, we need to make sure any regulatory decision about mifepristone is based on the science and the law – not the politics of the abortion debate.

Mr. SOUDER. Ms. Holmes Norton, do you have an opening statement?

Ms. HOLMES NORTON. Thank you very much, Mr. Chairman. Mr. Chairman, first, I want to say that if there is a drug, if it is a contraceptive drug, if it is a drug related in any way to the health of women, that scientists tell us causes death or injury of any kind, that drug should have no approval.

I don't think this committee is qualified to make that judgment. I think that judgment has to be committed to the kind of scientific study you would do if you were serious about these eight deaths. The most important thing we can do is to find out causation here, because then we know how to prevent the deaths or injury. Anything that stands in the way of that link is not a serious attempt to deal with it. Anything that jumps over the appropriate scientific inquiry is not serious about these eight deaths.

I think RU–486 has been very important in preventing abortions and in getting to where American women are going to get anyway. We simply will never be able to keep this kind of drug, which has not been shown to be harmful by scientists, out of the hands of people. So if it is going to get into the hands of people, one thing we want to know is what causes it.

What we don't want is to investigate scientists, for example, who give us answers contrary to our personal or moral or religious beliefs. We want to leave them free and unfettered to tell us what the scientific method reveals to them.

Finally, Mr. Chairman, I particularly regret not being able to stay throughout this hearing because of other hearings, but I do want to go on the record indicating the unthinkable series we have witnessed during this term that show the unmitigated politicization of the one area that Americans always held off from politics, and that is science itself. Whether Schiavo or creationism renamed intelligent design or stem cell research or, God help us, global warming itself, there are views floating around this Congress that essentially reach conclusions on these matters of huge scientific moment based on their own personal belief.

I never thought that the country that has stood at the forefront of science in the world would ever reduce science to personal, political, and religious views and opinions and I don't believe that, in effect, that is what the country is going to let us do when they see the long list before them of bills, of things we now can't do, of things we do do, only because of the personal, political, and religious views of some Members. When they see that the attempts that have been made during this session of Congress and during this administration to burden scientists with the personal views of Members of Congress, it is a shameful day for American science and I think we have to wipe it away if we do nothing else.

Thank you, Mr. Chairman.

Mr. SOUDER. Mr. Davis.

Mr. DAVIS OF ILLINOIS. Thank you very much, Mr. Chairman, and I shall be brief. Let me just thank you for calling this hearing. I think that every single one of us are indeed concerned about the health, safety, and well-being of every single individual as they make use of a drug, medical procedure, or pattern of treatment. I would hope especially given the fact that we are talking about safety of a drug, that we discuss and debate the science and not the ideological expressions of individuals who may be bent one way or another around the question and the issue of abortion.

And so I look forward to the witnesses and look forward to the information that is going to be presented and I yield back the balance of my time.

Mr. SOUDER. Mr. Ruppersberger.

Mr. RUPPERSBERGER. Thank you, Mr. Chairman, for having this hearing. We know the issue of abortion is a very difficult issue for many citizens in this country and there are different people that have different points of view. One of the issues it looks like—you can't hear? That is probably a good thing. [Laughter.]

Starting again, we know the abortion issue is a very difficult issue and we also know that individuals, no matter which side of the issue you are on with respect to abortion, is something that you are probably not going to change. It would be more positive for our whole country if we could come to some resolution, but I don't think that is going to happen.

But I think in today's hearing it is important that we really don't use the political issue of abortion but focus on this RU–486. With that in mind, RU–486 underwent a vigorous, a rigorous 4-year review process at the FDA, more rigorous than most drugs. As you know, it was considered under a select set of regulations called Subpart H, which allowed the FDA to add more conditions on the drug's distribution and use.

But since its approval in the year 2000, nearly 600,000 women in the United States have used RU–486. It has proven to be a safe and effective means of terminating early pregnancy. Because of this medical option, millions of women worldwide, including survivors of sexual assault, have had the right to end an early pregnancy with privacy and dignity.

Tragically, there have been four confirmed deaths in the United States from bacterial infection in women who used RU–486. At this point, we do not know what caused these infections or if these deaths are at all related to the use of RU–486.

Fortunately, the CDC and FDA have moved quickly to investigate these incidents. Early this month, RU–486 scientists from the Nation's leading public health agencies gathered in Atlanta to discuss the bacteria that caused these deaths and the risk it poses to pregnant women. Career scientists and doctors are the best equipped to investigate this issue and I know they will get to the bottom of it. We must rely on accepted medical standards for determining the safety and efficacy of a medication. The future of RU–486 should lie with the FDA and the medical community, not with Congress, who do not have yet the full picture and have scientific data before us to make a decision on women's health.

I yield back.

[The prepared statement of Hon. C.A. Dutch Ruppersberger follows:]

Congressman C.A. Dutch Ruppersberger
Committee on Government Reform

"RU-486 – Demonstrating a Low Standard for Women's Health?"

May 17, 2006

Statement:

I look forward to the testimony of our expert witnesses here today. I hope that we will be able to have an honest discussion about women's health.

RU-486 underwent a rigorous four-year review process at the FDA – more rigorous than most drugs. As you know, it was considered under a select set of regulations called "subpart H," which allowed the FDA to add more conditions on the drug's distribution and use.

Since its approval in 2000, nearly 600,000 women in the U.S. have used RU-486. It has proven to be a safe and effective means of terminating early pregnancy.

Because of this medical option, millions of women worldwide, including survivors of sexual assault, have had the right to end an early pregnancy with privacy and dignity.

Tragically, there have been four confirmed deaths in the U.S. from bacterial infection in women who used RU-486. At this point, we do not know what caused these infections or if these deaths are at all related to the use of RU-486.

Fortunately, the CDC and FDA have moved quickly to investigate these incidents.

Earlier this month, 486 scientists from the nation's leading public health agencies gathered in Atlanta to discuss the bacteria that caused these deaths and the risks it poses to pregnant women.

Career scientists and doctors are the best equipped to investigate this issue and I know they will get to the bottom of it.

We must rely on accepted medical standards for determining the safety and efficacy of a medication.

The future of RU-486 should lie with the FDA and the medical community, not with Members of Congress who do not yet have a full picture of the impact of RU-486 on women's health.

Mr. Chairman, I yield back.

Mr. SOUDER. Ms. Watson.

Ms. WATSON. I want to thank you, Mr. Chairman. I applaud the subcommittee for bringing this topic up to educate the American public.

It is very important that the FDA, our drug watchdog agency, is engaged with the scientific community and the population at large in order to provide informed choices for the women of the United States. Mifepristone, or RU–486, has been utilized for nearly two decades by women all over the globe. This drug provides an early abortion option that does not require surgery. It has been reported that since the FDA approved RU–486 in 2000, significantly more than half a million American women have used this medication.

Mr. Chairman, let us be very clear during this hearing today. Ideological debate pro or anti-abortion is a discussion that we have been afforded the free speech right to talk about. Medical process and drug effectiveness should not be subject to any debate of that style. It is imperative to the health of our Nation that Congress, the FDA, health care delivery professionals, and the scientific community and patients approach the utilization of any drug from an educated, scientifically tested, and unbiased perspective.

So I am interested to hear the testimony of our witnesses because oversight is a serious responsibility that we undertake on behalf of the American people, and the use of RU–486 is a subject that must be treated with unbiased integrity and regard for the overall health of women.

Four women have died of sepsis. All four were infected by the same type of bacteria. What does the medical and scientific community say to this situation? Is Mifeprex responsible? So our decision should be based on education and scientific investigation and I look forward to hearing about that information.

I yield back my time, Mr. Chairman. Thank you very much.

Mr. SOUDER. Thank you. Mr. Shays.

Mr. SHAYS. Thank you, Mr. Chairman. I want to thank you, one, for having a hearing on this issue, to encourage you to use that same logic to have a hearing on Plan B, which is a related drug that doesn't require an abortion but can accomplish the same task. I want to say that I have extraordinary respect for you, and in spite of your bias one way and my bias the other, I am convinced that this will be a fair hearing and I appreciate that.

I guess I would just end by saying that I appreciate particularly the thoughtful statement of your ranking member, Mr. Cummings, and the ranking member of the full committee. I think others have said the same thing, but I think they covered it well. If I could have written a statement in time, I would have been pleased to have written either of those two statements, so I would like to stand on their statements.

Again, thank you for allowing me to participate.

Mr. SOUDER. Thank you, and the record needs to show that there have been 8 women, at least, who have died, 950 adverse events, and not all are necessarily associated with the other infection.

Also, I would like to ban abortion, but this isn't about abortion. We can't ban abortion. This is a health question. Just because scientists disagree doesn't mean that one person is trying to put an ideological view on it and other people have a scientific view.

In a number of issues lately, I have been accused of being anti-science because the scientists I support disagree with the scientists who another group support. In fact, this drug was cleared in an expedited process, not using mostly U.S. research, and we have a right to look into this drug and we should be looking into this drug. Scientists disagree and we should hear the debate. Just because one group of scientists is political doesn't mean that the other group of scientists aren't political, too. We all know that science requires judgments, as well. If it was just an ideological view, we couldn't hold this hearing. We are not hearing from ideological people, we are hearing from medical people, we are hearing from researchers, and we will hear the debate and I am looking forward to that debate.

I ask unanimous consent that all Members have 5 legislative days to submit written statements and questions for the hearing record and that any answers to written questions provided by the witnesses also be included for the record. Without objection, it is so ordered.

I also ask unanimous consent that all exhibits, documents, and other materials referred to by Members and the witnesses may be included in the hearing record, that all Members be permitted to revise and extend their remarks, and without objection, it is so ordered.

Our first panel is composed of Janet Woodcock. Dr. Woodcock is Deputy Commissioner for Operations at the FDA. If you could come forward, remain standing. As an oversight committee, it is our standard procedure to swear in our witnesses. If you will raise your right hand.

[Witness sworn.]

Mr. SOUDER. Let the record show that the witness responded in the affirmative.

We thank you for coming today and we are looking forward to your testimony.

STATEMENT OF JANET WOODCOCK, M.D., DEPUTY COMMISSIONER FOR OPERATIONS, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. WOODCOCK. Good afternoon, Mr. Chairman, Congressman Cummings, and Members of the subcommittee. I am Janet Woodcock, Deputy Commissioner for Operations at the Food and Drug Administration. Today, I will discuss the approval history and the current regulatory status of the product Mifepristone, currently marketed in the United States under the trade name Mifeprex and indicated for termination of early pregnancy.

First, I would like to correct any misconceptions that may exist about the initial approval of the drug. Mifeprex was approved in September 2000 after extensive FDA review of the application, which included three adequate and well-controlled trials documenting the efficacy and safety profile of the drug when used for this indication. In addition, post-market experience in Europe included over 620,000 exposures for pregnancy termination, of which 415,000 were in combination with Misoprostol. These data fully conform with FDA's standards for approval.

In order to assure that Mifeprex was used by qualified specialists, FDA and the sponsor agreed that the drug would be approved under 21 CFR 314.520. This section of Subpart H concerns safety, not effectiveness. This infrequently used regulatory provision allows approval of a drug with restrictions to assure safe use. In this case, distribution of Mifeprex is restricted to physicians qualified to supervise medical abortion and its complications and who have agreed to fully inform patients and obtain their written agreement to provide an FDA-approved patient information sheet and agreed to report serious adverse events to the sponsor.

This product met the requirements of all applicable laws and regulations, including Subpart H. As FDA made clear in the preamble to the final rule, the Subpart H regulations were intended to apply to serious or life-threatening conditions, such as depression, not only to diseases. Approval of Mifeprex under restricted distribution had nothing to do with accelerated approval based on a surrogate end point, which is a separate provision of the regulations.

FDA has monitored reports of Mifeprex-related adverse events very carefully after marketing. As of March 31, 2006, 950 cases related to the approved use were submitted to FDA. Consistent with the clinical trials' experience and the drug label, heavy vaginal bleeding was the most frequently reported adverse event, with 422 cases, followed by incomplete abortion, with approximately 400 cases. Other serious events included 88 instances of infection, with 18 of them considered severe, and 27 ectopic pregnancies. This adverse event profile was consistent with prior experience with medical termination of pregnancy.

Since approval, FDA has evaluated nine reports of death in the United States potentially associated with the approved indication. Three of these have either been found or appear to be unrelated to medical abortion. An additional death was due to a ruptured ectopic pregnancy. The use of Mifeprex is contraindicated in ectopic pregnancy. Five deaths were due to a rapidly fatal toxin mediated shock syndrome. One of these was caused by infection with Clostridium Perfringens. The four additional deaths, all in California, were caused by infection with a rare anaerobic bacterium, Clostridium Sordellii. An additional Clostridium Sordellii fatality previously occurred in a clinical trial in Canada.

This rapidly fatal toxin mediated shock syndrome was not anticipated to be a complication of medical abortion. It has not been reported in the extensive European experience to date, estimated over 1.5 million uses of the drug. Eight previous U.S. cases of fatal shock due to C. Sordellii, primarily after vaginal delivery or Caesarian delivery, have been reported in the obstetrical literature.

FDA responded aggressively to the reports, with extensive follow-up and expert consultation. Last week, NIH, CDC, and FDA cosponsored a scientific workshop on potential emerging Clostridium infections. CDC researchers identified three additional C. Sordellii cases, two fatal, that occurred after spontaneous abortion. CDC has also instituted an investigation in California looking into 321 unexplained pregnancy-associated deaths between 2000 and 2003. They have excluded 303 cases from being related to toxic shock-related syndrome and are further investigating 18 more.

Given that the information on this infection and its epidemiology is still emerging, it is not possible at this time to determine whether the current Mifepristone/Misoprostol regimen for medical abortion results in an increased risk of C. Sordellii infection or whether the reporting requirements under the Mifeprex approval and subsequent intensive investigations have uncovered what is an emerging risk in pregnancy overall. FDA is collaborating with the CDC and NIH on further research into this infection and will continue to provide timely public information.

I will be happy to answer your questions.

[The prepared statement of Dr. Woodcock follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

JANET WOODCOCK, M.D.

DEPUTY COMMISSIONER FOR OPERATIONS

FOOD AND DRUG ADMINISTRATION
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

"RU-486: DEMONSTRATING A LOW STANDARD FOR WOMEN'S HEALTH?"

BEFORE THE

SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY AND HUMAN RESOURCES
COMMITTEE ON GOVERNMENT REFORM
HOUSE OF REPRESENTATIVES

MAY 17, 2006

FOR RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Janet Woodcock, Deputy Commissioner for Operations at the Food and Drug Administration (FDA or the Agency). From 1994 to 2005, I was Director of FDA's Center for Drug Evaluation and Research (CDER). During my tenure as CDER Director, the Agency approved the drug, mifepristone, U.S. brand name, Mifeprex.

Thank you for the opportunity to discuss the Agency's role in the approval process and post-marketing activities pertaining to mifepristone. My testimony also will address FDA's adverse event reporting system and the Agency's actions in responding to adverse events reported from use of mifepristone.

REVIEW AND APPROVAL OF MIFEPREX

FDA's review and approval of the Mifeprex application adhered strictly to our legal mandate and mission as a science-based public health regulatory agency. The Agency's review complied with the Federal Food, Drug, and Cosmetic (FD&C) Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the approved labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved. . ."

FDA's approval of the Mifeprex application was based on three "adequate and well-controlled" studies as that term is defined in Title 21, *Code of Federal Regulations* (CFR) section 314.126, applicable to new drug applications (NDAs) under 505(b)(1) of the FD&C Act. The Mifeprex NDA contained data from three clinical trials (a large U.S. trial and two French trials) and safety data from a post-marketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received the combination regimen of mifepristone together with the drug misoprostol). These data constituted evidence that mifepristone was safe and effective for its approved indication, the medical termination of intrauterine pregnancy through 49 days' pregnancy, in accordance with section 505(d) of the FD&C Act.

FDA's finding of drug effectiveness was based on a comparison to a historical control of the expected rate of continued pregnancy. In a historically controlled trial, listed in regulation as an acceptable type of control (see 21 CFR 314.126(b)(2)(v)), the results of treatment with the test drug are compared with experience derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies such as metastatic breast cancer and progesterone positive and unresectable meningiomas), and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

FDA's Reproductive Health Drugs Advisory Committee voted 6 to 0 (with two abstentions) on July 19, 1996, that the benefits of mifepristone exceeded the risks of the product. The Mifeprex NDA was subjected to all levels of review within CDER and was found to be safe and effective for its approved indication.

FDA's Subpart H Regulations

The Mifeprex application was approved on September 28, 2000, under FDA's Subpart H regulations (21 CFR part 314 Subpart H). FDA approved the Mifeprex NDA under Subpart H at the sponsor's request because the Agency determined that post-marketing distribution restrictions on the product were necessary to ensure its safe use.

Under section 314.520, if FDA concludes that a drug product shown to be effective can be used safely only if distribution or use is restricted, the Agency will require post-marketing restrictions. As part of the Subpart H approval for Mifeprex, distribution of the drug was restricted in several ways, including that it must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information about Mifeprex.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an

opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.

- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex package serial number in each patient's record.

There also were a number of restrictions relating to the physical distribution system for the product. These restrictions were designed to ensure the safe use of the drug. Some complications of medical abortion are similar to those of surgical abortion, and some of these require a surgical intervention. Comprehensive risk management of abortion therefore requires that the managing physician be able to diagnose an ectopic pregnancy, manage the risks of abortion, including bleeding and infection, and be able to conduct a surgical abortion if necessary or quickly refer a patient to a provider who is trained, qualified, and readily available to do so.

In addition to distribution restrictions, the sponsor agreed to conduct two post-marketing studies, also referred to as "Phase IV commitments." These two Phase IV studies consisted of a pregnancy outcome follow-up study of women who continued to be pregnant for at least one month after any Mifeprex exposure and a prescriber monitoring study. The prescriber monitoring study was designed primarily to assess the relationship between certain post-treatment adverse events and whether the prescriber (a) provided surgical intervention if the medical abortion was not successful or

(b) referred patients to another healthcare provider for surgical abortion if the medical abortion was not successful.

Danco Laboratories, the sponsor of the Mifeprex NDA, is currently conducting the pregnancy follow-up study; it has designed and implemented a protocol, but it has determined that as of this time very few pregnancies (less than 20) were continued. For the number that were continued, Danco informs the Agency it has been unable to collect outcome data on any of them because of difficulties enrolling patients. Danco has attempted to conduct the prescriber monitoring study and has designed and implemented a protocol to that effect; however, FDA understands Danco's efforts have revealed that (1) only about 10 percent of Mifeprex prescribers were willing to participate in the study and (2) of these, more than 90 percent stated they were able to perform surgical abortions (without referral to another healthcare provider) if needed to complete a medical abortion. Thus, Danco has been unable to recruit sufficient participants to adequately power the study; furthermore, it appears that a significant majority of prescribers themselves provide any necessary surgical interventions to their patients.

The Prescriber's Agreement

The approved labeling for Mifeprex includes a Prescriber's Agreement that each potential provider is required to sign before the sponsor will distribute the product. The Prescriber's Agreement addresses the areas of expertise of the provider, the required reporting of adverse events, and the need to obtain informed consent from the patient.

Medical Expertise of the Provider - The Prescriber's Agreement requires the provider to sign a form indicating that he or she meets the qualifications outlined in the form and that he or she will observe the guidelines stated in the form. This includes agreement with the following statement:

"Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex."

These restrictions are intended to ensure that Mifeprex is prescribed by persons who are qualified to manage early pregnancy and ensure patient access to surgical abortion if that becomes necessary. Additionally, the Prescriber's Agreement states that the patient's follow-up visit at approximately 14 days is important to confirm a complete termination of pregnancy and the absence of complications.

Reporting of Adverse Events - Providers who sign the Prescriber's Agreement agree to report to the sponsor all hospitalizations, transfusions, other serious adverse events and on-going pregnancies. Prescribers either report directly to Danco's Medical Director or use a Danco 1-800 number.

Patient Informed Consent - The Prescriber's Agreement further requires that the prescriber must, consistent with the guidelines, (1) provide each patient with a copy of the Medication Guide and the Patient Agreement, (2) fully explain the procedure to the patient, (3) give the patient the opportunity to read and discuss the Guide and Agreement, and (4) obtain the patient's signature on the Patient Agreement. The Medication Guide, which is part of the approved labeling for Mifeprex, is patient labeling designed to provide information necessary to patients' safe and effective use of the drug (see 21 CFR part 208).

Combination Regimen Including Use of Misoprostol Together with Mifepristone

FDA approved the Mifeprex NDA for the termination of early intrauterine pregnancy, defined as 49 days or less counting from the last menstrual period. The FDA-approved regimen for medical abortion consists of taking 600 milligrams (mg) (three 200 mg tablets) of mifepristone orally on Day 1 in the provider's office and 400 micrograms (mcg) (two 200 mcg tablets) of misoprostol orally on Day 3, also in the provider's office. A post-treatment examination is to be completed on approximately Day 14. FDA is aware that many medical practitioners use modified regimens, which may include prescribing different doses of mifepristone and misoprostol, dosing misoprostol on a different day, and/or advising patients that the misoprostol tablets be inserted into the vagina. While some of the modified regimens have been described in the medical literature, the safety and effectiveness of mifepristone and misoprostol dosing regimens other than the one in currently approved labeling have not been evaluated by FDA.

FDA is aware that questions have been raised about the use of misoprostol, a drug indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric ulcers, in the medical abortion regimen with mifepristone, without a separate approval and labeling of misoprostol for this use. There are numerous other examples where the labeling of one drug recommends its use with a second drug without the approval of the sponsor of the second drug. The Agency routinely approves new drugs to be used with products already approved without requiring a change to the labeling of the previously approved drug. For example, several beta blockers and Angiotensin-converting Enzyme (ACE) inhibitors are approved for use in heart failure and in all cases, use with diuretics is recommended even though the diuretics themselves have not been separately approved for use in heart failure and do not claim this use in their labeling. The labeling for Carvedilol indicates the drug for use in treating certain types of heart failure, usually in addition to diuretics, an ACE inhibitor, and digitalis, to increase survival and decrease hospitalization.

Use of Ultrasound and Ectopic Pregnancies

In the U.S. clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, pregnancies also can be dated using other clinical methods. As mentioned previously, part of the restricted distribution of Mifeprex includes that each provider physician must state that he or she has the ability to assess accurately the duration of pregnancy and to diagnose ectopic pregnancy. The Agency determined that it was neither appropriate nor necessary for it to mandate how physicians clinically assess their patients for duration of pregnancy and for ectopic pregnancy. The approved labeling for Mifeprex recommends ultrasound evaluation as needed, leaving this decision to the physician.

Information on ectopic pregnancy was added to the WARNINGS section of the approved label in November 2004 to further alert physicians to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy, particularly given that some of the expected symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy. The revised label stated that:

> "No causal relationship between these events and Mifeprex and misoprostol has been established. Mifeprex is already contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifeprex is not effective for terminating these pregnancies. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex."

Age of Patients Using Mifepristone

The clinical trials in the NDA excluded patients younger than 18 years old, and the labeling states that the safety and efficacy in this age group have not been studied. FDA did not require studies in pediatric patients. In the case of Mifeprex, there was no scientific reason to expect menstruating females under 18 years of age to have a different physiological outcome with the approved Mifeprex regimen from women 18 years of age and older. Since the approval of Mifeprex, literature has been published supporting the safety and effectiveness of mifepristone in females under age 18 (see Phelps R.H. et al., "Mifepristone abortion in minors" *Contraception* 64:339-43(2001)).

FDA'S ADVERSE EVENT REPORTING SYSTEM

FDA approves a new drug application if a sponsor demonstrates, through required clinical trials, that a product is safe and effective for its intended uses. The limited populations of clinical trials, however, usually do not generate all of the information about risks of a new product. Adverse effects not detected during clinical trials frequently are identified after approval through reporting to manufacturers or directly to FDA, observational studies based on more widespread use of the product after approval, or through post-marketing clinical-trials. To account for this need, FDA created the Adverse Event Reporting System (AERS), a post-marketing drug safety program designed to collect and assess adverse events identified after approval for all drugs regulated by the Agency.

AERS consists of data from the Spontaneous Reporting System, a forerunner of the current AERS database (for reports from 1968 to October 1997) and data from AERS (for reports from November 1997 to present). AERS is a surveillance system that relies on voluntary reporting of adverse events to FDA by health care professionals and consumers, as well as reporting (some voluntary, some required by regulation) by pharmaceutical manufacturers. It includes reports from the United States and other countries of serious adverse events, non-serious adverse events, labeled adverse events (adverse events that are listed in a drug's approved labeling), and unlabeled adverse events, as well as unlabeled adverse events attributed to a drug in post-marketing clinical trials. It generally does not contain reports from clinical trials conducted prior to the approval of a product. As of April 2006, AERS contained approximately 3.5 million reports for all drugs.

When evaluating reports from the AERS system, it is important to recognize several caveats. First, accumulated case reports cannot be used to calculate actual incidences of adverse events or estimates of risk for a product, as the reporting of adverse events is a voluntary process with inherent underreporting. Reporting to the AERS database is influenced by other factors such as duration of marketing, market share, publicity about an adverse reaction, and regulatory actions. Additionally, the AERS database often contains multiple reports of the same incident.

When FDA receives a report of a serious adverse event, the Agency carefully analyzes the available scientific information to determine whether or not the serious adverse event or death is related to the use of any of the drugs listed as possible medications. FDA staff physicians and epidemiologists evaluate the reports, investigate the seriousness of the health hazard and, if necessary, issue warnings and initiate corrective actions.

AERS Reports for Mifepristone

A total of 1,024 mifepristone *reports* have been received since the drug's approval on September 28, 2000, through March 31, 2006. However, it is important to distinguish between the total number of *reports* and the total number of *cases*, where one case refers to the collection of all reports pertaining to a single incident in a single patient. Duplicate reports often occur because the same event in the same patient is reported from more than one source (e.g., a physician sends the report directly to FDA as well as to the company, which in turn sends the report to FDA). Of these 1,024 post-marketing adverse event reports, after FDA accounted for duplicate reports, reports for use of mifepristone for indications other than termination of pregnancy (for example, treatment of certain cancers, or use in men or infants), and reports from outside the U.S., there were 950 *cases* involving mifepristone use in the U.S. in women for termination of pregnancy.

With regard to adverse event reports listing mifepristone as a possible medication, FDA has reviewed the database, identified duplicate reports, and in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details. Thus, the numbers below may differ from the numbers of the reports that may be obtained through Freedom of Information Act requests. Also, please note that these events cannot with certainty be causally attributed to mifepristone because of information gaps about patient health status, clinical management of the patient, concurrent drug use, and other possible medical or surgical treatments.

Nine hundred fifty (950) cases in women who had taken mifepristone for medical termination of pregnancy were received by FDA through March 31, 2006. According to Danco, approximately 575,000 women have been exposed to mifepristone since its approval. Most of the 950 cases listing mifepristone as a possible medication initially were submitted to FDA by the sponsor, with only 11 reports initially received by FDA directly from patients, health care providers, investigators, attorneys or family members. Approximately one-quarter of the 950 patients were hospitalized. The most frequently reported event of interest in the case reports was blood loss requiring a transfusion. The next most frequently reported events were infection and ectopic pregnancy. Approximately 40 percent of the reported 950 cases were received from three states, with 163 cases initially reported from California, 117 from New York, and 103 from Arizona, for a total of 383 cases. Approximately 94 percent of cases occurred in women aged 18 years or older, with an average age of 27 years, median age of 26 years, and a reported age range of 13-46 years. Age was unspecified in 3.8 percent of reported cases.

Cases of Heavy Bleeding

FDA has identified 116 *cases* documenting that the patient received a blood transfusion due to heavy bleeding after medical abortion. The Mifeprex U.S. labeling includes a specific warning about this adverse event in a BOXED WARNING and in the WARNINGS section.

Deaths Reported After Use of Mifepristone

FDA is aware of 12 deaths possibly involving the use of mifepristone in women. Nine of these deaths were in the U.S. Of these, five were determined to be related to infections, one involved an undiagnosed ectopic pregnancy, one appears unlikely to be related to the use of mifepristone, one was determined to be unrelated to either the medical abortion or the use of mifepristone and misoprostol, and one that is currently under investigation appears not to have involved the administration of misoprostol and appears to be unrelated to the use of mifepristone. In addition, there were three deaths in other countries related to mifepristone and misoprostol induced abortion. These 12 deaths are described below:

- Five deaths in U.S. women associated with mifepristone and misoprostol induced medical abortion, with what appears to be a rapidly fatal toxin-mediated shock syndrome
    - Four of these five, all in California, were confirmed to involve a rare anaerobic bacterium, *Clostridium sordellii (C. sordellii).* All involved the use of mifepristone 200 mg orally, followed by 800 mcg of misoprostol inserted intravaginally, a regimen that is not part of the FDA-approved labeling.
    - One U.S. woman from the west, whose death was confirmed to involve a different bacterium, *Clostridium perfringens* (*C. perfringens*). This case involved the use of mifepristone 200 mg orally, followed by 800 mcg of misoprostol inserted intravaginally, a regimen that is not part of the approved labeling.
- One death in a U.S. woman who had an undiagnosed ectopic pregnancy. Ectopic pregnancy is a contraindication for the use of mifepristone.
- One death involving a woman who initially had an unsuccessful attempted surgical abortion, followed by an unsuccessful medical abortion involving mifepristone, and then followed by a

second and successful surgical abortion. The woman was hospitalized approximately one month after taking mifepristone, and she died approximately 24 hours after admission during a hysterectomy. There was no autopsy, but pathology findings included a degenerated, pus-filled uterine fibroid. Cultures were negative for any Clostridial bacteria. Based on the available evidence at this time, FDA and the Centers for Disease Control and Prevention (CDC) do not believe this death was related to the use of mifepristone.

- One death in the northeastern U.S. was determined to be unrelated to either the medical abortion or the use of mifepristone and misoprostol.
- One death in the southwestern U.S. is still under investigation, but appears not to have involved the administration of misoprostol, and appears to be unrelated to the medical abortion or the use of mifepristone.
- One death in Canada of a woman who died during participation in a clinical trial. This death was due to sepsis involving *C. sordellii.*
- One death in Sweden of woman as a result of severe hemorrhage related to a medical abortion.
- One death of a British woman was attributed to gastric (stomach) bleeding from an ulcer.

The four California deaths, plus the Canadian case, were reported in the New England Journal of Medicine in December 2005, by CDC scientists. Since that time, CDC has been actively seeking additional cases across the country. FDA is aware that CDC has identified two additional cases which appear to be unrelated to the use of mifepristone:

- A death from the midwest in a woman who had a second trimester medical abortion employing misoprostol and laminaria (a moisture absorbing medical device inserted into the vagina to stimulate cervical dilation), but not mifepristone. This woman had *C. perfringens.*

- A toxin-mediated infectious death due to *C. sordellii* in a woman who initially was reported to have had a medical abortion. However, the woman had appendicitis and pneumonia, not a uterine infection, and CDC has been unable (despite extensive investigation) to find evidence that she had an abortion or had ever been pregnant.

The cases of women with *C. sordellii* infection are of great concern to FDA and CDC. *C. sordellii* is a rare infection and has been reported in the literature since the 1930s. The largest case series, published in 1989 by McGregor, Soper, and colleagues in the obstetrical literature, describes cases after vaginal delivery and Cesarean section, as well as a case of spontaneous endometritis. All developed a fatal shock syndrome. Other literature describes infectious illnesses in intravenous drug users and in organ transplant recipients.

FDA'S RESPONSE TO SAFETY CONCERNS RELATED TO MIFEPRISTONE

FDA has been following and evaluating safety concerns about mifepristone since its approval. As a result of ongoing monitoring of safety issues associated with mifepristone, FDA approved two revisions to the Mifeprex drug labeling and Medication Guide, in November 2004 and in July 2005. In November 2004, the black box warning was revised and strengthened to add new information on the risk of serious bacterial infections, sepsis, bleeding, and death that may occur following any termination of pregnancy, including use of Mifeprex. In July 2005, FDA approved a labeling supplement to again strengthen the black box warning on the product by noting that "atypical presentations of serious infection…can occur without fever, bacteria or significant findings on pelvic exam…." and to advise patients to seek immediate medical attention if they experience prolonged heavy bleeding.

The nature of the infection-related deaths led FDA to test for evidence of contamination in the manufacturing lots of Mifeprex and misoprostol used by the four women who died in California. The restricted distribution program for Mifeprex allowed FDA to identify the specific manufacturing lots that were involved in each case. No evidence of contamination was found and all cultures were negative.

FDA has issued public health advisories in connection with safety concerns related to mifepristone in 2004, 2005, and most recently in March 2006. FDA has consistently highlighted the fact that the cases of severe infection occurred with regimens of mifepristone and misoprostol that were not in approved labeling, although the relationship of the infections to such use remains unknown.

FDA has sought expert advice and consultations to evaluate scientific issues from both inside and outside the Agency. To supplement the ongoing evaluation and expertise of CDER's Office of Drug Safety and Division of Reproductive and Urologic Products, FDA consulted with its Division of Anti-Infective Drug Products. FDA also consulted with outside obstetricians/gynecologists and maternal-fetal medicine experts and CDC, ultimately leading to the detailed microbiology testing and documentation of *C. sordellii* as the underlying organism involved in the four cases from California. These cases have led to CDC investigations across the country in search of additional cases, including their initiation of a detailed search concerning all maternal deaths in the state of California. These investigations are ongoing, but the national search for *C. sordellii* cases in association with maternal death has already identified, in addition to those described above with medical abortion, three cases in women who recently had a miscarriage (spontaneous abortion). These occurred in the midwestern, western, and northeastern U.S.

It is noteworthy that over the time period that *C. sordellii* was being identified as a source of rare, infection-related deaths following medical abortion, CDC was investigating unusual outbreaks of another Clostridium species, *Clostridium difficile (C. difficile)*. Unlike *C. sordellii*, *C. difficile* is a common infection in the U.S., with an estimated incidence of up to 500,000 cases per year, mostly in hospitals and following use of antibiotics. The infection, which also is mediated by a toxin produced by the bacterium, typically causes severe diarrhea and fever. In recent years, however, cases associated with a severe, sepsis-like illness have increasingly been reported, and most recently such cases have been reported in healthy individuals, four in pregnant women, with no recent hospitalization or history of antibiotic use, suggesting a newly emerging serious toxin-mediated illness (with many similarities to the fatal cases of *C. sordellii*).

To help address the questions and issues that would allow for a better understanding of *C. sordellii* infection, it was clear to FDA that expertise in other Clostridial diseases and microbiology, as well as experts on the effects of drug exposure in both conditions, was essential. This led FDA to initiate a scientific workshop in collaboration with CDC and the National Institute for Allergy and Infectious Diseases to bring together such scientific and public health experts. It was clear to FDA and its sister agencies that all involved needed to collaborate to better understand the risk factors contributing to reports of morbidity and mortality associated with *C. sordellii* and *C. difficile*, and that further research was likely to be needed. This workshop, "Emerging Clostridial Diseases," was held Thursday, May 11, 2006, in Atlanta, Georgia.

Emerging Clostridial Diseases Workshop

The goal of this public workshop was to identify research needs and priorities in order to enable progress in understanding the virulence, pathogenesis, host factors, and nonantimicrobial risk factors contributing to reports of morbidity and mortality associated with *C. sordellii* and *C. difficile*. Three panels, consisting of medical and/or public health representatives from federal government (FDA, CDC, and the National Institutes of Health), state governments, and academia, presented data and discussed a number of the complex issues surrounding these two related anaerobic bacteria.

1. **Clinical Syndromes, Pathophysiology and Host Factors** – Nine presenters discussed various clinical aspects of both *C. sordellii* and *C. difficile*.
2. **Surveillance for Disease and Sources of Infection** – Two presenters discussed related disease surveillance initiatives at both the federal and state levels
3. **Identifying a Research Agenda** – The final discussion consisted of a general discussion among workshop presenters, as well as the audience, regarding recommendations for research agenda priorities for:

- Surveillance and epidemiology;
- Basic research; and
- Diagnosis, treatment, and prevention.

There appeared to be broad consensus that additional research is necessary to improve our clinical understanding of both *C. sordellii* and *C. difficile*. Participants also stressed that surveillance and communication efforts should continue to be refined and focused on enhancing the epidemiological data about, and awareness among clinicians of, both diseases. The workshop served as an important first step in advancing our understanding of some of the most critical underlying questions surrounding mifepristone, *C. sordellii*-related deaths, and a potential association between the two. It also underscored the fact that there are additional important questions to be asked and clinically investigated regarding, for example, toxin production and potential antibiotic use in association with mifepristone. While an exact pathway forward, and a precise timeline, are unclear at this point, FDA is committed to continuing to work with others, both within and outside of the federal government, to improve our knowledge of these dangerous diseases and the public health concerns they raise.

CONCLUSION

FDA's mission is to protect and promote the public health by ensuring that marketed drugs are safe and effective for their approved indications. The American people have come to expect this gold standard, and the Agency remains dedicated to fulfilling this important responsibility. FDA is a science-based public health regulatory agency, and the foundation of the drug approval process is sound scientific rigor. FDA takes all reports of adverse events seriously, and the Agency finds none more troubling than reported grave injuries to, or deaths of, otherwise healthy patients. Mifeprex post-marketing adverse event data are being evaluated on an ongoing basis. These data will continue to inform the risk-benefit profile of this drug, including consideration of the risks associated with other alternatives. FDA will continue to communicate to the public, healthcare practitioners, and patients emerging safety information that becomes available that would assist them in making proper choices regarding their health.

Mr. SOUDER. Let me ask this first question as a multi-part. This drug went through a different type of an approval process than others, Subpart H in the approval process, and it allows the FDA to impose certain restrictions on the distribution of Mifeprex, which you covered in your written testimony. How do you monitor Danco's compliance with each of these restrictions and what do you do when they are not in compliance? Furthermore, are they absolutely required to report all the incidents?

Dr. WOODCOCK. Yes. FDA has, once the drug was approved under these provisions, put into place an inspectional system for FDA to inspect the manufacturer to assure they were complying with the provisions of the approval, and we have done frequent inspections to oversee their compliance with this program.

Mr. SOUDER. And are they required under the law to report all adverse effects?

Dr. WOODCOCK. All manufacturers are required under the law to report adverse events that they find out about with drugs that they manufacture or distribute to the FDA.

Mr. SOUDER. Are you tracking that?

Dr. WOODCOCK. Yes.

Mr. SOUDER. And then if you are, how did the manufacturer not know about some of the things that you referred to, or did you discover those through the manufacturer? Have they reported any of these? Do you view them as cooperative?

Dr. WOODCOCK. The vast majority of reports that we have received, which are over 1,000, counting duplicates, have come directly from the manufacturer. The physicians who have signed the physician agreement are instructed to report adverse events to the manufacturer.

Mr. SOUDER. We heard a number of the opening statements refer to that there is a regimen, but yet RU–486 is frequently used past the 49 days as it is recommended and it is administered at a dosage of 200 rather than the FDA-approved 600 dosage. It is often prescribed without the required patient agreement form and its counterpart, Misoprostol, is used vaginally despite its approval for oral use only. Furthermore, although the manufacturer is required to have the ability to track its use to the patient level, the manufacturer estimates to arrive at usage rates for the purposes of safety and promotional material, WHO, Planned Parenthood, and a number of these are not following your regimen. Would it be fair for one to conclude from this evidence that RU–486 is not being used according to the restriction that you imposed on it in Subpart H?

Dr. WOODCOCK. There is no restriction in the approval letter or in the physician agreement that says the physician must use a specified dose or regimen. The manufacturer, who FDA regulates, is complying with the restrictions that were placed on the drug distribution at the time of approval.

Mr. SOUDER. So you are saying that individuals are—let me ask this. Would it be fair for one to conclude that the restrictions placed on RU–486 have failed to ensure that the drug will be used in a manner consistent with the FDA's opinion on safe use? In other words, when you cleared the drug, it was cleared on the basis of the usage. Now what you are telling me is there is no checking to see that it is being used in the way you approved it, and could not that explain some of the problem?

Dr. WOODCOCK. The restriction program was pub in place to ensure that physicians who prescribe the drug could date a pregnancy—that is a very important aspect of using this regimen—could rule out with professional experience an ectopic pregnancy, and were manage the complications of medical abortion, which include requirements for surgical intervention. So that was the purpose of the restriction program.

FDA reviews data that is submitted to it when FDA approves a dose and a regimen in an approved indication for use of the drug. Subsequently, based on medical literature, physicians may deviate from the recommended dose and this occurs very frequently. The restricted distribution program had to do with distribution to physicians who were qualified. So the drug is not available in pharmacies. It cannot be prescribed by physicians who are not qualified and have not gone through the program.

Mr. SOUDER. So let me see if I can understand, see if this is an oversimplification of what you just said. You said you tested it with one regimen. Then you didn't put that in force because you concluded after the tests, based on information that regimen wasn't essential to the safety of the individuals?

Dr. WOODCOCK. FDA——

Mr. SOUDER. Because the regimen dealt with other subjects other than the safety.

Dr. WOODCOCK. FDA reviewed the data based on the safety and effectiveness information that was included in the application. That was the recommended regimen, the approved regimen that is in the drug label. The patient agreement and so forth discuss that regimen. All the approved patient labeling discusses that regimen. It is quite common in the United States, however—a recent article showed that about 21 percent of drug usage in the United States deviates somewhat from the label directions——

Mr. SOUDER. Let me, because my time is up, when I came as a freshman, I was vice chair of Mr. Shays' subcommittee and I remember on the secondary use of drugs one of the huge questions is the FDA, however, does not give its blessing to non-approved regimens and non-prescribed ways of doing it. And I would also like to insert in the record at this point a history of other drugs where with one or two deaths, they have been pulled off the market. Usually, scientific research does not go forth while there is a question on a drug, and I think an exception has been made in this for political reasons. It is exactly the reverse of what has been charged.

[The information referred to follows:]

Lower Standards for RU-486? [1]

RU-486
FDA has acknowledged the **deaths of eight women associated with the drug, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection.**[2] These and other cases have added up to a total of **950 adverse event reports** (AERs) as of March 31, 2006. These reports are based on the FDA's Adverse Event Reporting System, a voluntary system, with inherent underreporting.

Compare the adverse events associated with RU-486 with those of other drugs:

NeutroSpec
December 19, 2005 – Palatin Technologies voluntarily suspended sales and marketing of NeutroSpec. No definitive determination was made regarding the relationship between NeutroSpec and reported adverse events.

Tysabri
February 28, 2005 – Biogen voluntarily suspended marketing of the drug as well as its use in clinical trials until more detailed information could be gathered on one death and one other adverse event.

Palladone
July 13, 2005 – Purdue Pharma agreed to voluntarily suspend sales and marketing of Palladone in the US. "To date, FDA is not aware of any patients who had life-threatening side effects from drinking alcohol while taking Palladone."

Cylert
May 2005 – Abbott chose to stop sales and market on Cylert. "FDA was aware of 13 reports of liver failure resulting in liver transplant or death…" "…the reporting reate for liver failure with pemoline is 10 to 25 times greater than the background rate of liver failure in the general population." NOTE: RU-486 is 10 to 14 times more lethal to the mother than surgical abortion during the first 49 weeks of gestation when RU-486 is used in chemical abortions.

Bextra
April 7, 2005 – Pfizer voluntarily withdraws Bextra from the U.S. market. FDA had concluded that the overall risk versus benefit profile of Bextra was unfavorable. "The reporting rate to FDA's spontaneous reporting system for these serious skin reactions was significantly greater for Bextra than other COX-2 selective agents."

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[1] Data extracted from a letter from David W. Boyer, Assistant Commissioner for Legislation, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 16, 2006) (on file with Subcommittee).

[2] Letter from David W. Boyer, Assistant Commissioner for Legislation, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 2, 2006) (on file with Subcommittee).

Vioxx
September 30, 2004 – Merck voluntarily withdraws Vioxx from US market. FDA was in the process of reviewing the cardiovascular events to determine whether labeling changes were warranted when Merck decided to withdraw it.

Orlaam
August 23, 2003 – Roxane stated that it was discontinuing the sale and distribution of the product after current inventory was depleted following reports of severe cardiac-related events among opiate-addicted patients.

Baycol
August 8, 2001 – Bayer Pharmaceuticals voluntarily withdrew the product after FDA received reports of 31 deaths associated with the drug.

Raplon
March 27, 2001 – Organon announced it was voluntarily withdrawing the drug after receiving reports of five deaths occurring during the administration of the drug.

Lotronex
November 28, 2000 – Glaxo Wellcome informed FDA it was voluntarily withdrawing Lotronex, after FDA received a total of 70 cases of serious adverse events, of which 34 required hospitalization without surgery, 10 resulted in surgical procedures, and three resulted in death.

Rezulin
March 21, 2000 – Manufacturer agreed to withdraw Rezulin after the drug showed it was more toxic to the liver than two other drugs.

Trovan
June 1999 – FDA issued a public health advisory when it received over 100 reports of patients who were ill with symptoms of liver toxicity. FDA was aware of 14 cases in patients whose livers actually failed.

Duract
June 22, 1998 – Wyeth-Ayerst announced it was withdrawing the analgesic, Duract, following reports of rare severe liver failure in patients in whom the drug was used for extended periods of time which was not in accordance with labeling instructions.

Tegison
March 1998 – Hoffman-La Roche voluntarily discontinued marketing Tegison because the product posed a greater risk of birth defects than a replacement product.

Mr. SOUDER. I yield to Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman.

First of all, thank you for being with us, Dr. Woodcock. Dr. Woodcock, there have been allegations that there was something unusual about the approval of Mifeprex. You were the Director of the Center for Drug Evaluation and Research back then, is that not correct?

Dr. WOODCOCK. That is true.

Mr. CUMMINGS. And did the FDA treat Mifeprex using the appropriate scientific and legal standards for safety and efficacy?

Dr. WOODCOCK. We used the scientific and legal standards that we use for every drug that we evaluate.

Mr. CUMMINGS. Now, anti-choice advocates have criticized the approval on a number of grounds, including the fact that there was no double-blind placebo controlled study of this drug. But it is hard for me to imagine how someone could conduct a placebo-controlled study of an abortion drug. That would mean giving the women seeking an abortion a placebo that would not terminate the pregnancy, is that right?

Dr. WOODCOCK. I suppose. The need for a placebo occurs when there is a tremendous variability in the outcome, and so you can't tell whether the outcome was due to the intervention or other events. For many types of interventions, such as anesthesia, all right, we don't have a randomized control group because you can easily tell whether people are unconscious and they don't become unconscious spontaneously very often. The same is true for contraceptives, where we have a very good background rate of pregnancy with unprotected intercourse. So in various situations, a totally accurate control is what is called a historical control, where we know what happens in that situation without an intervention.

Mr. CUMMINGS. There seems to be confusion about the way that Mifeprex was approved. It was approved under provisions known as Subpart H, is that correct?

Dr. WOODCOCK. Yes.

Mr. CUMMINGS. Some of these provisions provide for an accelerated approval of drugs for life-threatening conditions. But a different part of Subpart H guides not expedited approval but the restricted distribution of certain products. Why was Subpart H used in the case of Mifeprex?

Dr. WOODCOCK. For Mifeprex, it was felt important that the distribution be limited to qualified practitioners, because although the intervention was found to be safe and effective, it was in the hands of individuals in the clinical trials who were able to diagnose pregnancy and date it properly, who were able to rule out ectopic pregnancy with a high degree of accuracy, and who were able to deal with the complications of medical abortion, including incomplete abortion. The drug would not be safe in the hands of practitioners who did not routinely take care of pregnant women, for example. So that is why these restrictions were put into place.

Mr. CUMMINGS. So this had nothing to do with accelerating approval?

Dr. WOODCOCK. Nothing to do with it. The evidence on effectiveness for Mifeprex was submitted in three trials that FDA found to be adequate and well-controlled trials for the purpose of demonstrating termination of pregnancy.

Mr. CUMMINGS. Well, the marketing application was submitted in March 1996, is that correct?

Dr. WOODCOCK. Yes.

Mr. CUMMINGS. But the drug wasn't approved until September 2000. That is like 4½ years later. The average time for approval is about 18 months, is that correct?

Dr. WOODCOCK. Yes.

Mr. CUMMINGS. So why did the approval process take so long?

Dr. WOODCOCK. FDA asked many questions and subjected this application, everything from the manufacturing of the drug, the pharmacology, the distribution of the drug, and the safety and efficacy to a very thorough review, such as we would for any drug, and in this case, it took that long.

Mr. CUMMINGS. I mean, what is the record, do you know, length of time?

Dr. WOODCOCK. Longer.

Mr. CUMMINGS. All right. I see my time is about up so I will submit questions.

Mr. SOUDER. Let me ask Congresswoman Schmidt and Congressman Shays, did you want to ask questions of this witness?

Mrs. SCHMIDT. I do.

Mr. SOUDER. Do you have questions, as well, Mr. Shays?

Mr. SHAYS. I don't want to ask her to have to stay after an hour of hearings after our votes.

Mr. SOUDER. We are going to have about an hour's worth of votes, so Mrs. Schmidt, why don't you ask some of your questions here.

Will you answer any written questions that we give you from the different Members, because it is going to be a long voting stretch, probably at least an hour here.

Dr. WOODCOCK. Certainly.

Mr. SOUDER. Mrs. Schmidt.

Mrs. SCHMIDT. Thank you, Mr. Chairman. What I am understanding is that there are seven deaths recorded from this drug. As a woman, why aren't we pulling this drug from the market?

Dr. WOODCOCK. You have to distinguish, first of all, and I know it is very confusing, you have to distinguish reports to the FDA, deaths that are actually occurred or related to administration of the drug in some way, and then where there is a causal relationship between administration of the drug and the death.

FDA actually has nine reports of death related to medical abortion in the United States. Three of those we find unrelated to administration of the drug. In one case, we cannot—either the patient is not documented to have taken the drug or other reasons unrelated. One death was due to ruptured ectopic pregnancy. Ruptured ectopic pregnancy, if the patient doesn't seek medical care rapidly, can be fatal. The ectopic pregnancy itself was a preexisting condition, was not caused by administration of Mifepristone and Misoprostol.

There were five deaths were due to sepsis, to infection, and what we don't know is whether or not medical abortion increases the probability of getting this infection. This infection has occurred after vaginal delivery, after Caesarian section, and after spontaneous abortion or so-called miscarriage, and there are documented cases in each of those instances. So we do not know if in medical abortion there is an increased rate of this infection or whether or not we are simply seeing these because of our intense scrutiny of outcomes after medical abortion due to the restricted distribution.

Mrs. SCHMIDT. May I have a followup, sir? I am having a problem with your explanation and I will tell you why. The ectopic pregnancy, the drug should never have been administered if she had an ectopic pregnancy, period, case closed. I don't care what the reason why the drug was administered. It was administered wrongly. That woman died because of it. So there is a problem.

But more importantly, the five of the infections, just because you don't know how the infection occurred, we do know they took the drug and they died. To me—I am from a farm community—it sounds like you need to pull the drug until you can be absolutely sure that there are no deaths related.

I have a whole list here of drugs that have been pulled from the market either voluntarily or involuntarily. There has just been a contact solution that has been pulled from the market because of serious eye infection, including the loss of sight. So we are real careful about other things about our body, but when it comes to a woman's body, I am just finding a problem that we are just not that careful.

I think this drug needs to be pulled from the market. It needs to be pulled from the market now and it is time that the FDA does something about it.

Mr. SOUDER. Thank you. We will send you some additional questions. May I ask you quickly, the FDA reported 116 cases of blood transfusion. Do you believe Mifeprex caused these hemorrhage cases?

Dr. WOODCOCK. Hemorrhage is a common complication of childbirth, spontaneous abortion, surgical abortion, and medical abortion. So when a woman is pregnant, she faces a possibility of experiencing hemorrhaging after childbirth and so forth. Yes, we expected——

Mr. SOUDER. So you believe these were common hemorrhaging cases, not extraordinary hemorrhaging cases?

Dr. WOODCOCK. It was expected and was observed in the clinical trial. There was a case of needing transfusion, so it was expected that some women after the medical abortion regimen would have bleeding requiring transfusion. That is correct.

Mr. SOUDER. So you believe that 116 cases in 575,000 is roughly similar to the population that would normally have it?

Dr. WOODCOCK. Yes. We feel that all the side effects except the Sordellii are within what we would expect in this population.

Mr. SOUDER. Thank you. We will submit——

Mr. SHAYS. Mr. Chairman.

Mr. SOUDER. Yes, Mr. Shays.

Mr. SHAYS. If I could submit questions in writing, because I do have questions. I just don't want to hold her for an hour.

Mr. SOUDER. OK.

Mr. SHAYS. So I will have questions. I will submit them through you.

Mr. SOUDER. Thank you.

Mr. SHAYS. Thank you.

Mr. SOUDER. The subcommittee stands recessed until we get back from votes.

[Recess.]

Mr. SOUDER. The subcommittee is back in session.

If the second panel could come forward. The second panel is Monty Patterson, father of Holly Patterson, who was 18 years old when she died taking RU–486; Dr. Susan Wood, former FDA Assistant Commissioner for Women's Health; Dr. Lisa Rarick, RAR Consulting; Dr. Donna Harrison, a member of the Mifeprex Subcommittee of the American Association of Prolife Obstetricians and Gynecologists; and law professor O. Carter Snead from the University of Notre Dame, former general counsel for the President's Council on Bioethics.

As an oversight committee, it is our customary practice to swear in each of the witnesses. Will you raise your right hands.

[Witnesses sworn.]

Mr. SOUDER. Let the record show that each of the witnesses responded in the affirmative.

We thank you each for coming. Thank you for your patience of putting up with the congressional procedure of having multiple amendments and bills. It makes for a long afternoon but one that we can never predict when we schedule a hearing.

We will start with Mr. Patterson. Thank you for coming, and once again, we express from all of us in the committee our sympathies for the loss of your daughter.

STATEMENT OF MONTY L. PATTERSON, LIVERMORE, CA

Mr. PATTERSON. Thank you very much. First of all, I just want to show you a picture of Holly so you know that we are talking about my daughter and who she is.

Mr. SOUDER. Why don't you pull the mic closer to you.

Mr. PATTERSON. I said I wanted to show you a picture of my daughter so at least you see what I have lost and actually what she lost.

I owe and dedicate my presence here to those who have no voice and particularly to my daughter, Holly, who died at 18, and the other women who have died or have been seriously hurt by taking the RU–486 medical abortion drug regimen as a solution to their unplanned pregnancy.

I am here to testify about my personal experience as the father of a victim of this drug and my consequent knowledge, experiences, and views pertaining to RU–486, the drug. I want to be clear that my views and testimony should be divorced from any debate about abortion. I feel we must examine the dangers associated with RU–486 for early medical pregnancy termination that are separate and apart from any particular view about a women's right to access and choice.

Twelve days after Holly's 18th birthday, on September 10, 2003, she walked into a Planned Parenthood clinic to be administered an RU–486 medical abortion regimen. By the 4th day, she was admitted to the emergency room of a local hospital. She was examined.

She was given pain killers. She complained of bleeding, cramping, constipation, and pain, but subsequently, she was sent home.

Seven days after taking RU–486, Holly returned to the same emergency room hospital complaining of weakness, vomiting, abdominal pain. Hours later, I was called to the hospital, where I found her surrounded by doctors and nurses, barely conscious and struggling to breathe. Holly was so weak she could barely hold onto my hand. Feeling utter belief and desperation, I watched Holly succumb to a massive bacterial infection as a result of a drug-induced abortion with RU–486.

With the support of my family and friends, I have spent thousands of hours researching medical and scientific journals, talking to doctors, legislators, State and Federal agencies, and to learn about the drug RU–486, otherwise known as Mifepristone.

I believe that RU–486 is the substantial contributing factor responsible for Holly's death. Currently, there have been eight deaths reported by the FDA linked with the drug. Furthermore, there are 900 or more serious health consequences associated with RU–486.

One year after Holly's death, I met with FDA and White House officials, in September 2004, to discuss concerns over the drug's safety and health issues. Two months later, the FDA announced additional black box warnings highlighting serious infections and death.

On May 11, 2006, I attended the CDC-FDA-NIH scientific conference in Atlanta whose main purpose was to discuss the safety of the drug regimen RU–486 to terminate early pregnancies. I presented a compilation of nearly 400 medical and scientific publications as a result of my 2½ years of extensive research. It is my hope this work will help to facilitate the understanding and causal relationship of RU–486 and medical abortion infections. Medical experts, Dr. Esther Sternberg, Dr. James McGregor, and Dr. Ralph Miech presented their concurring studies that RU–486 has serious and lethal medical implications as evidenced through animal models. I have brought that disk here today for the subcommittee for their review.

The FDA is responsible for protecting public health and, therefore, must reconsider the use of RU–486 in early medical pregnancy terminations. It should explore active epidemiology and study animal models that show the alteration of the immune response by its reaction with RU–486 as it relates to serious and lethal infections. The FDA needs to provide the medical community reliable means and methods to recognize cases of serious adverse events associated with RU–486. Finally, the FDA needs to implement a confident reporting apparatus of these events so they can accurately evaluate the safety and health consequences with the use of the drug.

Patients, families, and their physicians are entitled to have all the information necessary to make informed choices. The safety, health, and welfare of women considering medical abortion with RU–486 is paramount and should not be jeopardized with a drug that can seriously cause them harm or death. Women have paid the ultimate price with their health and their lives. How many must die needlessly before this drug is removed from the market?

Women have been and are still relying upon what they think is truthful information concerning the limited risk involved with a medical abortion. Yet, does the average patient, a teenager like Holly, understand she may be risking her life taking RU–486 when she is repeatedly exposed to statements like, “It is what women have wanted for years. It is the first FDA-approved pill providing women with a safe and effective non-surgical option for ending early pregnancy.”

There are no quick fixes or magical pills to make an unplanned pregnancy go away. My family, friends, and community were deeply saddened and are forever marred by Holly’s preventable and tragic death. It is my vibrant memory of Holly and her premature death that have inspired me to make the public aware of the serious and lethal effects of the RU–486 regimen. Not a day goes by that I do not recall her brilliant blue eyes, engaging smile, laughter, and sheer gentle beauty.

Holly’s personal drive and unwavering determination continue to inspire me and give me strength to pursue these critical issues in her name. It is a natural instinct to protect our loved ones and speak for those who cannot speak for themselves. Thank you.

Mr. SOUDER. Thank you, and thank you for your willingness to speak out.

[The prepared statement of Mr. Patterson follows:]

Subcommittee on Criminal Justice, Drug Policy & Human Resources
Hearing entitled "RU-486 – Demonstrating a Low Standard for Women's Health?"
May17, 2006

Testimony of Monty L. Patterson
Livermore, California
montypatterson@comcast.net

Introduction

I owe and dedicate my presence here to those who have no voice, particularly to my daughter, Holly, who died at 18, and the other women who have died or have been seriously hurt by taking the RU-486 medical abortion drug regimen as a solution to an unplanned pregnancy.

I am here to testify about my personal experience as the father of a victim of this drug and my consequent knowledge, experiences, and views pertaining to RU-486, the drug. I want to be clear that my views and testimony should be divorced from any debate about abortion. I feel we must examine the dangers associated with RU-486 for early medical pregnancy termination that are separate and apart from any particular view about a woman's right to access and choice.

Personal Experience

Twelve days after Holly's 18th birthday, on September 10, 2003, she walked into a Planned Parenthood Clinic, to be administered a RU-486 medical abortion regimen. By the fourth day she was admitted to the emergency room of a local hospital complaining of bleeding, cramping, constipation, and pain. Holly was examined, given painkillers, and then sent home. Seven days after taking RU-486, Holly returned to the same emergency room hospital, complaining of weakness, vomiting, and abdominal pain. Hours later, I was called to the hospital, where I found her surrounded by doctors and nurses, barely conscious and struggling to breathe. Holly was so weak she could barely hold on to my hand. Feeling utter disbelief and desperation, I watched Holly succumb to a massive bacterial infection, as a result of a drug-induced abortion with RU-486.

Issues

With the support of my family and friends, I have spent thousands of hours researching medical and scientific journals, talking to doctors, legislators, state and federal agencies to learn about the drug RU-486, otherwise known as mifepristone.

I believe that RU-486 is the substantial contributing factor responsible for Holly's death. Currently, there have been 8 deaths reported by the FDA linked with RU-486. Furthermore, there are over 900 reported serious health consequences associated with the drug.

FDA & White House

One year after Holly's death, I met with FDA and White House officials in September 2004, to discuss concerns over the drug's safety and health issues. Two months later the FDA announced additional black box warnings highlighting serious infections and death.

CDC/FDA/NIH Conference

On May 11, 2006 I attended the CDC/FDA/NIH scientific conference in Atlanta whose main purpose was to discuss the safety of the drug regimen RU-486 to terminate early pregnancies. I presented a compilation of nearly 400 medical and scientific publications as a result of my 2 ½ years of extensive research. It is my hope this work will help to facilitate the understanding and causal relationship of RU-486 and medical abortion infections. Medical experts, Dr. Esther Sternberg, Dr. James McGregor, and Dr.

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FDA Responsibility

The FDA is responsible for protecting public health and therefore, must reconsider the use of RU-486 in early medical pregnancy terminations. It should explore active epidemiology and study animal models that show the alteration of the immune response by its interaction with RU-486 as it relates to serious and lethal infections. The FDA needs to provide the medical community reliable means and methods to recognize cases of serious adverse events associated with RU-486. Finally, the FDA needs to implement a confident reporting apparatus of these events so they can accurately evaluate the safety and health consequences with the use of the drug.

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Conclusion

Women have been and are still relying upon what they think is truthful information concerning the limited risks involved with a medical abortion. Yet, does the average patient, a teenager, like Holly, understand she may be risking her life taking RU-486 when she's repeatedly exposed to statements like: "It's what women have wanted for years: Its the first FDA approved pill providing women with a safe and effective non-surgical option for ending early pregnancy".

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Holly's personal drive and unwavering determination continue to inspire me and give me strength to pursue these critical issues in her name. It is a natural instinct to protect our loved ones and speak for those who can not speak for themselves.

Mr. SOUDER. Dr. Wood.

STATEMENT OF SUSAN F. WOOD, FORMER ASSISTANT COMMISSIONER FOR WOMEN'S HEALTH AND DIRECTOR OF THE OFFICE OF WOMEN'S HEALTH, FOOD AND DRUG ADMINISTRATION

Ms. WOOD. Thank you, Mr. Chairman, and thank you, members of the subcommittee. My name is Susan Wood and for the last 15 years, I have worked in women's health policy within the Federal Government. In each of my positions, I have advocated for the promotion of women's health through increased research, services, and prevention.

From November 2000 through August 2005, I was the Assistant Commissioner for Women's Health and Director of the Office of Women's Health at the U.S. Food and Drug Administration. Prior to that, I was Director of Policy and Program Development at the Department of Health and Human Services Office on Women's Health.

But I began my work in women's health in 1990 as congressional staffer for the bipartisan Congressional Caucus for Women's Issues. My scientific training is as a Ph.D. in biology and my research focused on basic cell biology and biochemistry, carried out at Boston University and at Johns Hopkins University School of Medicine.

Over the last 15 years, I have been proud to be part of the following advances we have made in women's health: expanded research at the NIH in areas such as breast and ovarian cancer, osteoporosis, heart disease, HIV/AIDS, and menopause; more inclusion of women in clinical research studies funded by NIH and regulated by the FDA; increased screening of women for cancer and for sexually transmitted diseases that lead to infertility; better quality mammography; coverage for preventive screenings by Medicare; and improved prevention and services for victims of domestic violence.

While I was at FDA, the Office of Women's Health supported groundbreaking research, including research on medications taken during pregnancy, to help find out about the proper doses of different medications that should be taken during the different stages of pregnancy. We also funded important health outreach programs in areas such as safe medication use, diabetes, menopause, and hormone therapy. The office also worked to implement and track the inclusion of women in clinical studies reviewed by FDA and to ensure the analysis of the data for important sex differences in safety and efficacy.

These advances and more were made through the concerted efforts of Members of Congress, the various agencies of the Department of Health and Human Services, the research and clinical communities, and women's health advocates across the country. One of the core principles that led to this progress was and remains ensure that we move forward based on the best available scientific and medical evidence, and when that evidence is lacking, go out and do the studies necessary to get it.

My commitment to women's health is founded on these scientific principles, knowing that this is the best way to expand our knowledge and improve the health of women and men both here in the

United States and abroad. My commitment to women's health, particularly to drug safety, is also founded in personal experience. I lost my much-loved sister to cancer at age 34, caused directly by a drug given to our mother while she was pregnant, the drug DES, also known as diethylstilbestrol. I can assure you that my commitment to drug safety for women is deeply felt and always at the forefront of my mind.

I appreciate your invitation to testify before this subcommittee on the issue of Mifepristone and whether or not FDA has held this drug to the best standard of review on safety and efficacy.

Let me point out that Mifepristone is not Plan B emergency contraception, which prevents unintended pregnancy and the need for abortion, but Mifepristone, RU–486, is a medication that causes abortion in the first few weeks of pregnancy.

Now, I was working at the Department of Health and Human Services Office on Women's Health at the time of the Mifepristone review. I, therefore, have no direct knowledge of the evaluation and the review that was happening at FDA, and that is exactly how it should be. The FDA was working independently, reaching its conclusions and decisions based on its usual processes and evaluation of the data. In fact, there was curiosity among many of us at the Department level about the subject, but we were given clear instruction by senior management of the Department that we were not to inquire, even informally, of our women's health colleagues at FDA about the status of the Mifepristone application. This was to ensure that there was not even a perception of Departmental influence on this highly visible application.

Upon my arrival at FDA in the fall of 2000 as head of women's health there, this independence of decisionmaking was confirmed to me by the professional staff that was directly involved in the review. The evidence presented to the FDA and the subsequent experience with the marketed product in the United States tells us that this is a safe and effective method for early termination of pregnancy.

Now, the recent deaths due to Clostridium Sordellii in women who have had a medical abortion are truly tragic and I do offer my sincere condolences to Mr. Patterson, his family, and the families of all the women. These deaths due to this bacterial infection have put us on notice that health professionals and women need to be aware of this potential risk.

More importantly, the close surveillance of adverse events associated with the use of Mifepristone have alerted us that this bacterial infection is present and caused the death of other women who have given birth or had a miscarriage—more, in fact, than the number of women who underwent a medical abortion. This pattern of infections and deaths after pregnancy is indeed disturbing and tells us once again that we need to do more to ensure safe pregnancy and safe motherhood. This is not limited to women who have been exposed to Mifepristone, and to focus solely on the women who have had a medical abortion is to miss the real threat to the health of women.

Our surveillance systems for maternal mortality and morbidity have been limited over the years due to limited funding and lower priority. These systems need to be improved and expanded to capture not only the impacts of Clostridium, but also so that we can understand and prevent the other risks that women face with pregnancy.

With Mifepristone, we can be confident that we have identified all or most of the adverse events and deaths. We cannot say the same for infections and deaths caused by C. Sordellii in women who have given birth or had a miscarriage, and those numbers may indeed be higher.

I applaud the CDC, FDA, and NIH for holding the scientific meeting on May 11th to begin the process of examining the data that we currently have on the nature of these infections, potential strategies for prevention, early detection, and effective treatment, and the research agenda that needs to be undertaken to answer the critical questions that exist. Although I did not attend, I understand that meeting participants presented current information and discussed the future needs to address this emerging infection.

Questions have been raised about whether Mifepristone is involved through changes of the immune system. These are serious questions that need to be studied, but at this point do not seem to be the compelling mechanism. Experts at CDC, FDA, and NIH reviewed the current information and appear to recognize that the infections and death due to C. Sordellii are not due to a simple drug effect. Rather, this is a complex situation that involves multiple factors that are linked to pregnancy. Getting to the bottom of what puts women at risk for this infection and what can be done to prevent and treat it is of the highest importance.

The experts at the meeting last week identified several clear areas of research that are needed, including improved surveillance of infection in women who have given birth or had a miscarriage, improved diagnosis, the role of antibiotics, the possible development of an antitoxin or other therapies, and further research on the nature of the Clostridium bacterium itself.

I strongly urge the subcommittee to support this research and surveillance agenda to address this threat to women's health. By doing so, we can improve the health outcome of all pregnant women and also help ensure improved maternal outcomes. Please do not allow politics to trump science once again when the health of women is at stake. Thank you.

Mr. SOUDER. Thank you.

[The prepared statement of Ms. Wood follows:]

Testimony of
Susan F. Wood, PhD
May 17, 2006

Subcommittee on Criminal Justice, Drug Policy, and Human Resources
Committee on Government Reform
US House of Representatives

Chairman Souder and Members of the Subcommittee:

My name is Susan F. Wood, PhD and for the last 15 years I have worked in women's health policy within the Federal Government. In each of my positions I have advocated for the promotion of women's health, through increased research, services and prevention. From November of 2000 through August of 2005, I was the Assistant Commissioner for Women's Health and Director of the Office of Women's Health at the US Food and Drug Administration. Prior to that, I was Director of Policy and Program Development at the Department of Health and Human Services Office on Women's Health. I began my work in women's health in 1990 as Congressional staff to the bipartisan Congressional Caucus for Women's Issues, initially as a fellow in the program sponsored by the American Association for the Advancement of Science, and then as professional staff to the Caucus. My scientific training is as a PhD in Biology and my research focused on basic cell biology and biochemistry carried out at Boston University and at Johns Hopkins University School of Medicine.

Over the last 15 years, I am proud to have been part of the advances we have made in women's health: expanded research at the NIH in areas such as breast and ovarian cancer, osteoporosis, heart disease, HIV/AIDS and menopause; more inclusion of women in clinical research studies funded by NIH and regulated by FDA; increased screening of women for cancer and for sexually transmitted diseases that lead to infertility; better quality mammography; coverage for preventive screenings by Medicare; and improved prevention and services for victims of domestic violence.

While I was at the FDA, the Office of Women's Health supported groundbreaking research, including research on medications taken during pregnancy to help find out what the proper doses of different medications should be during the different stages of pregnancy. We also funded important health outreach programs in areas such as safe medication use, diabetes, and menopause and hormone therapy. The Office also worked to implement and track the inclusion of women in clinical studies reviewed by FDA and to ensure the analysis of the data for important sex differences in safety and efficacy.

These advances and more were made through the concerted efforts of Members of Congress, the various agencies of the Department of Health and Human Services, the research and clinical communities, and women's health advocates around the country. One of the core principles that led to progress was and remains: ensure that we move forward based on the best available scientific and medical evidence. And when that evidence is lacking: go out and do the studies necessary to get it.

My commitment to women's health is founded on these scientific principles, knowing that this is the best way to expand our knowledge and improve the health of women and men both here in the US and abroad.

My commitment to women's health, particularly to drug safety, is also founded in personal experience. I lost my much loved sister to cancer at age 34, caused directly by a drug given to our mother while she was pregnant, the drug diethylstilbestrol – known as DES. I can assure you my commitment to drug safety for women is deeply felt and always at the forefront of my mind.

I appreciate your invitation to testify before this subcommittee on the issue of mifepristone and whether or not FDA has held this drug to the best standard of review on safety and efficacy.

I was working in the DHHS Office on Women's Health at the time of the mifepristone review, and therefore have no direct knowledge of the evaluation and review that was happening at the FDA. That is exactly as it should be. The FDA was working independently, reaching its conclusions and decisions based on its usual processes and evaluation of the data. In fact, there was curiosity among many of us at the Department level about the subject, but we were given clear instruction by senior management at the Department that we were not to inquire, even informally, of our women's health colleagues at FDA about the status of the mifepristone application. This was to ensure that there was not even a perception of Departmental influence on this highly visible application. Upon my arrival at FDA in the fall of 2000, this independence of decision-making was confirmed to me by the professional staff that was directly involved in the review. The evidence presented to FDA and the subsequent experience with the marketed product in the US tells us that this is a safe and effective method for early termination of pregnancy.

The recent deaths due to Clostridium sordellii in women who had had a medical abortion are truly tragic. I offer my sincere condolences to Mr. Patterson, his family, and the families of all of the women. These rare deaths due to this bacterial infection have put us on notice that health professionals and women need to be aware of this potential risk.

More importantly, the close surveillance of adverse events associated with the use of mifepristone have alerted us that this bacterial infection is present and has caused the deaths of other women who have given birth or had a miscarriage – more in fact than the number of women who underwent a medical abortion. This pattern of infections and death after pregnancy is indeed disturbing, and tells us once again that we need to do more to ensure safe pregnancy and safe motherhood. This is not limited to women who have been exposed to mifepristone, and to focus solely on women who have had a medical abortion is to miss the real threat to the health of women. Our surveillance systems for maternal mortality and morbidity have been limited over the years due to limited funding and lower priority. These systems need to be improved and expanded to capture not only the impacts of Clostridium, but also so that we can understand and prevent the other risks that women face with pregnancy. With mifepristone we can be confident that we have identified all or most of the adverse events and deaths. We cannot say the same for infections and deaths caused by C. sordellii in women who have given birth or had a miscarriage.

I applaud the CDC, the FDA and the NIH for holding the scientific meeting May 11, 2006 on Clostridium infections, to begin the process of examining the data that we currently have on the nature of these infections, potential strategies for prevention, early detection and effective treatment, and the research agenda that needs to be undertaken to answer the critical questions that exist. Although I did not attend, I understand that the meeting participants presented current information and discussed the future needs to address this emerging infection.

Questions have been raised about whether mifepristone is involved through suppression of the immune system. This is a question to be studied, but at this point does not seem to be a compelling mechanism. If the immune system were suppressed, we would also expect to see a rise in other more common infections. Also, although progesterone suppresses the immune system normally in pregnancy, mifepristone is an anti-progestin and might be expected to counter this normal suppression of the immune system. We would also expect to have seen this infection in places using the higher doses of mifepristone, but, in fact, use in the US is of a much lower dose (usually one-third) than that commonly used in Europe. Similarly we would expect to see this infection in cancer patients who have used mifepristone over longer periods of time. This pattern thus far has not emerged.

Experts at CDC, FDA and NIH reviewed the current information and appeared to recognize that the infections and deaths due to C. sordellii are not due to a simple drug effect. Rather this is a complex situation that involves multiple factors that are linked to pregnancy. Getting to the bottom of what puts women at risk for this infection, and what can be done to prevent and treat it, is of the highest importance.

The experts at the meeting last week identified several clear areas of research that are needed, including improved surveillance of infection in women who have given birth or had a miscarriage, improved diagnosis, the role of antibiotics, the possible development of an antitoxin or other therapies, and further research on the nature of the Clostridium bacteria. We need to know what makes this strain toxic: is it interactions with the environment; why are these deaths thus far localized in the west; and what in pregnancy or in the woman's body leads to production of the toxin? I strongly urge the Subcommittee to support this research and surveillance agenda to address this threat to women's health. By doing so, we can improve the health outcome of all pregnant women and also help ensure improved maternal outcomes. Please do not allow politics to trump science once again when the health of women is at stake.

Mr. SOUDER. Dr. Rarick.

STATEMENT OF LISA D. RARICK, M.D., RAR CONSULTING, LLC

Dr. RARICK. Good afternoon, and thank you, Mr. Chairman and members of the subcommittee, for the opportunity to provide testimony in this important discussion of the use of Mifepristone for medical abortion.

My name is Lisa Rarick. I am a medical doctor with training and board certification in obstetrics and gynecology. I received my medical degree from Loma Linda University School of Medicine and my OB/GYN training at Georgetown University. After my residency, I remained on the faculty of the Department of OB/GYN at Georgetown and soon also began to work at the U.S. Food and Drug Administration.

Although my work at the FDA began as a part-time position in the Center for Drug Evaluation and Research looking into fetal effects of drug exposure, I quickly grew interested in CDER's broader mission of protecting and promoting public health through pharmaceutical regulation.

I transitioned to full-time employment at the FDA by September 1989. My work at CDER progressed from the review and analysis of fetal exposure information to work as a primary medical reviewer, also called medical officer, for new drugs in the Division of Metabolic and Endocrine Drug Products. As a medical officer, I had responsibility for the review of investigational and approved drugs used in various conditions for women's health.

In 1996, a new division, the Division of Reproductive and Urologic Drug Products, was created. I was named as its first Director. During that time, I was well acquainted with the application for Mifepristone and participated in the review as well as the Advisory Committee meeting discussions regarding this product. I was actively involved in the regulatory actions taken for this product during my tenure as Division Director.

By the year 2000, I continued to move up CDER's organizational ladder in various positions and I spent my final year at the FDA, July 2002 to July 2003, in FDA's Office of Women's Health.

My conclusions after review of the available scientific information regarding Mifepristone while at the agency, as well as my subsequent review, are consistent with the FDA's conclusions. The approval of Mifepristone in September 2000, more than 4 years after its application was submitted, was based on more than the necessary number of studies submitted and reviewed by the division of which I was Director. As many are aware, an application submitted to the FDA to support a new drug approval must contain adequate and well-controlled studies to confirm efficacy and safety. Generally, the word "studies" is interpreted as requiring two adequate studies. Although there are some instances where one study is acceptable, most applications contain the usual two confirmatory clinical trials. In the case of Mifepristone, three studies were submitted in order to establish efficacy and safety for early intrauterine pregnancy termination.

The clinical review of this product included an analysis of all human studies utilizing Mifepristone, including these three large Phase 3 studies involving close to 2,500 women. The Reproductive

Health Drugs Advisory Committee was convened in 1996 and asked to discuss and provide recommendations during the review of this application. The committee reviewed these Phase 3 studies. They also heard from over 30 speakers during the open public hearing portion of that meeting. They recommended by a vote of six-to-nothing, with two abstentions, that benefits exceeded risk.

The approval action taken by the agency in September 2000 utilized the regulatory option of Subpart H restrictions for this product. Contrary to the assertion that Subpart H designation was based on a desire for accelerated approval of Mifepristone, this is clearly not the case. In this case, the application of Subpart H regulations actually provided FDA with more rigorous oversight and allowed for the formal imposition of restricted distribution. In essence, a Subpart H approval is meant to restrict the use of Mifepristone, not accelerate its availability.

Clearly, since approval, the FDA has remained extremely vigilant in its regulatory oversight of Mifepristone. The labeling has been revised three times since its year 2000 approval. Each of these labeling change actions followed a complete FDA review of the clinical studies and post-marketing information available for Mifepristone and resulted in updated presentations of scientific information for consideration by prescribers and patients. Labeling revisions such as these are an important and expected part of drug regulation and indicate active and appropriate review of post-approval information.

As with any medication, when reports of serious adverse events associated with Mifepristone use are received by FDA, they are carefully analyzed and rigorous investigation is employed to ascertain the relationship, if any, between the drug and the event as well as to ascertain mechanisms to prevent similar events in the future.

I applaud the FDA's efforts to better understand the recent findings of serious bacterial infection reported in a small number of women after Mifepristone use and in other pregnancy-related conditions. In particular, as you have heard, the FDA, CDC, and NIH held a joint meeting on May 11th of this year. This meeting was an effort in which experts came together to better understand reports of morbidity and mortality associated with Clostridial infections. My understanding from those who attended the meeting is that the rare cases of Clostridial infection and death reported in Mifepristone users are, at this time, not explained by a simple drug-based association. In fact, the presentations and the discussion made it clear that these infections are occurring in various pregnancy-related conditions, not only post-abortion settings.

I say this not to dismiss the fact that some infections are occurring in women who have chosen medical abortion but to emphasize that the agencies must and are looking at the infection trends more broadly. Further investigation and understanding of these infections and various pregnancy-related outcomes is essential.

In conclusion, I urge this subcommittee to allow the FDA to continue to do its job. There is no evidence that FDA is shying away from the difficult questions of risk and benefit for this indication. Risks are being investigated. Adverse event reporting for medical abortion is uncovering and forcing investigation of previously unexplored risks related to pregnancy and post-pregnancy events. Let us all continue to support the FDA and others as they fulfill their mission to protect and promote the public health.

The public can only have confidence in the FDA's conclusion if it knows that it is impervious to political pressure. I urge us to resist the temptation to interfere in this instance and instead for Congress to allow the dedicated public health professionals at the FDA to do their jobs, continue their investigations, and take any actions that might be needed to protect and promote women's health. Thank you.

Mr. SOUDER. Thank you.

[The prepared statement of Dr. Rarick follows:]

Lisa D Rarick, MD
RAR Consulting, LLC
Reproductive Health and Regulatory Affairs
215 Midsummer Circle
Gaithersburg, MD 20878
301.548.9750
rarick215@comcast.net

Written Testimony/Prepared Statement re:
"RU-486: Demonstrating a Low Standard for Women's Health?"
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Hearing date May 17, 2006

Good afternoon and thank you, Mr. Chairman and members of the subcommittee, for the opportunity to provide testimony in this important discussion of the use of mifepristone for medical abortion.

My name is Lisa Rarick. I am a medical doctor with training and board certification in Obstetrics and Gynecology. I received my medical degree from Loma Linda University School of Medicine in 1984 and my Ob/Gyn training at Georgetown University 1984-88. After my residency, I remained on the faculty of the Department of Ob/Gyn at Georgetown and soon also began to work at the US Food and Drug Administration (FDA).

Although my work at the FDA began as a part time position in the Center for Drug Evaluation and Research (CDER) looking into fetal effects of drug exposure (Accutane and seizure medications were the main focus of this work in the late 1980's), I quickly grew interested in CDER's broader mission of protecting and promoting public health through pharmaceutical regulation.

I transitioned to part-time clinical practice and full time employment at the FDA by September of 1989. By 1993 I was no longer involved in individual patient care. I maintain my medical license with both the State of Maryland and the District of Columbia and my Ob/Gyn board certification through the American Board of Obstetrics and Gynecology.

My work at CDER progressed from the review and analysis of fetal exposure information to work as a primary medical reviewer (also called Medical Officer) for new drugs in the Division of Metabolic and Endocrine Drug Products. As a Medical Officer I had responsibility for the review of investigational and approved drugs used in various conditions for women's health.

In 1996 a new Division (the Division of Reproductive and Urologic Drug Products) was created. I was named as its first Division Director and remained in that position for the next 3.5 years (June 1996-Dec 1999). During that time I was well acquainted with the application for mifepristone and participated in the review as well as the Advisory Committee meeting discussions regarding this product. I was actively involved in the regulatory actions taken for this product during my tenure as Division Director. In December, 1999 I moved up CDER's organizational ladder from Division to Office level and became the Deputy Office Director for the Office of Drug Evaluation 2. This Office did not have responsibility for the mifepristone application. After a year at the Office level I took a position with the Center Director's Office (under the direction of Dr. Janet Woodcock) as the Associate Director for Quality Assurance. Among other things, this office was charged with implementing "good review practices" across the entirety of the Center for Drug Evaluation and Research.

I spent my final year at the FDA (July 2002-July 2003) in the Office of Women's Health in the Office of the Commissioner under the directorship of Dr. Susan Wood. Since leaving government service in the summer of 2003 I have provided consulting services to pharmaceutical companies, venture capital, advocacy groups and individuals regarding regulatory affairs and reproductive health.

My conclusions after review of the available scientific information regarding mifepristone while at the Agency as well as my subsequent review are consistent with the FDA's conclusions. The approval of mifepristone in September, 2000 was based on more than the necessary number of studies submitted and reviewed by the division of which I was director. As many are aware, an application submitted to the FDA to support a new drug approval must contain adequate and well-controlled studies to confirm efficacy and safety. Generally the word "studies" is interpreted as requiring two adequate studies. Although there are some instances where one study is acceptable,[1] most applications contain the usual two confirmatory clinical trials. In the case of mifepristone, three studies were submitted in order to establish efficacy and safety for early intrauterine pregnancy termination.

The clinical review included analyses of all human studies utilizing mifepristone including these three Phase 3 studies involving close to 2500 women. The Reproductive Health Drugs Advisory Committee was convened and asked to discuss and provide recommendations during the review of this application. The Committee reviewed the two Phase 3 studies conducted in France as well as preliminary US clinical study information in 1996. They also heard from over 30 speakers during the Open Public Hearing portion of that meeting. They recommended by a vote of 6-0 (with 2 abstentions) that benefits exceeded risk.

The approval action taken by the Agency in September, 2000 utilized the regulatory option of "subpart H" restrictions for this product. Contrary to the assertion that the subpart H designation was based on a desire for "accelerated" approval of mifepristone, this is clearly not the case. The application for marketing of mifepristone was submitted in March, 1996 and approved in September of 2000. Certainly FDA, pharmaceutical companies and other interested parties can agree that a review and approval process of 4 plus years does not meet any regulatory definition of "fast" or "accelerated". In this case, the application of subpart H regulations actually provided FDA with more rigorous oversight and allowed for the formal imposition of restricted distribution. As per the regulation (21 CFR 314.500-314.560), one application of the subpart H regulations allows for approval in situations "when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted". Subpart H approval also allows for more oversight of promotional materials and a streamlined mechanism for withdrawal procedures. In essence, the subpart H approval was meant to restrict the use of mifepristone, not "accelerate" its availability.

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[1] Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" May 1998

Clearly, since approval, the FDA has remained extremely vigilant in its regulatory oversight of mifepristone. The labeling has been revised three times since its year 2000 approval. Each of these labeling change actions followed a complete FDA review of the clinical studies and postmarketing information available for mifepristone and resulted in updated presentations of scientific information for consideration by prescribers and patients. Labeling revisions such as these are an important and expected part of drug regulation and indicate active and appropriate review of post-approval information.

As with any medication, when reports of serious adverse events associated with mifepristone use are received by FDA, they are carefully analyzed and rigorous investigation is employed to ascertain the relationship, if any, between the drug and the event, as well as to ascertain mechanisms to prevent similar events in the future. I applaud the efforts of the FDA to better understand the recent findings of serious bacterial infection reported in a small number of women after mifepristone use and in other pregnancy-related conditions.

In particular, as you know, the FDA, Centers for Disease Control and Prevention (CDC) and the National Institutes of Health-National Institute of Allergy and Infectious Disease (NIH-NIAID) held a joint meeting on May 11 of this year. This meeting was an effort in which experts came together to better understand reports of morbidity and mortality associated with clostridial infections. My understanding from those who attended the meeting is that the rare cases of clostridial infection and death reported in mifepristone users are, at this time, not explained by a simple drug-based association. In fact, the presentations and discussion made it clear that these infections are occurring in various pregnancy-related conditions, not only post-abortion settings. I say this not to dismiss the fact that some infections are occurring in women who have chosen medical abortion, but to emphasize that the agencies must—and are—looking at the infection trends more broadly. Further investigation and understanding of these infections in various pregnancy-related outcomes is essential. Although we in the scientific community must be open to all possibilities—and I believe we are—to date no evidence has emerged to support the hypothesis that mifepristone interferes with the immune response and thus allows for widespread multi-organ infection in women. Immune suppression-associated infection in this setting would not appear as reports of the appearance of one organism, but would present as infections with any or all of the various bacteria present in the female reproductive tract. In addition, this infection has not been reported in patients with known immune suppression such as those with HIV, cancer, or those who are on immunosuppressive drug regimens. Again, we should not close off consideration of any serious hypothesis, but to date the hypothesis that mifepristone itself is a cause of these infections is not supported by the data.

As I mentioned earlier, the FDA is actively investigating reports of death and serious adverse reactions with mifepristone. CDER is charged with a mission to protect and promote the public health through regulation of pharmaceuticals. The medical review team for mifepristone (both pre- and post-approval) was and is clearly aware of the science and results assessing both risks and effectiveness of the use of mifepristone for the medical termination of early intrauterine pregnancy. In other words, the system is working; investigation is underway, I urge Congress to allow the agencies to continue their work.

I would also like to say a word about medications and risk, generally. As for any medical procedure or treatment, the review and analysis of medical abortion must be seen in the context of approved alternatives. For many diagnoses multiple options exist for treatment—each with differing risk profiles. For example, in the arena of women's health—endometriosis and fibroids, while once conditions treated primarily through surgical means, now have approved pharmaceutical treatment options. Men were once faced with only device and surgical options for management of erectile dysfunction. I believe we are all aware that medical options now exist. Prostate, cervical cancer and breast cancer patients are faced with decisions of benefits and risks regarding options of surgery, medication, radiation and sometimes combination treatments or other modalities. All of these various methods for treatment offer different risk/benefit considerations. One modality is not considered "best" for any specific condition, but all modalities must be considered and applied to the individual case decision.

Women and couples are faced with complex decisions when it comes to pregnancy termination—not only terminations in the context of unintended pregnancies, but also in the case of non-viable pregnancies and in the management of spontaneous abortion ("miscarriage"). Clearly mifepristone offers a safe alternative to surgical abortion. Every option available to pregnant women presents different risks and benefits. Medical abortion is one option for those who choose or require early pregnancy termination. FDA clearly believes, as I do, that women and their providers must be well-informed regarding risks of medical abortion. This belief is based on the principle of informed consent, which states that before any medical care is delivered, the patient must be informed about the risks, benefits, and alternatives, and understanding those facts, must give consent. I believe informed consent for mifepristone is being adequately provided through the process the FDA imposed on the medication with its approval. Specifically, the approval of mifepristone included mandated FDA-approved prescribing information, FDA-approved Medguide,[2] and a patient agreement form. In my experience, these restrictions on a medication are unusual and, in my view, are one indication of many that the FDA is taking its oversight responsibilities seriously.

In conclusion, I urge this subcommittee to allow the FDA to continue to do its job. There is no evidence that FDA is shying away from the difficult questions of risk and benefit for this indication. Risks are being investigated. Adverse event reporting for medical abortion is uncovering and forcing investigation of previously unexplored risks related to pregnancy and post-pregnancy events. Let us all continue to support FDA and others as they fulfill their mission to protect and promote the public health. The public can only have confidence in the FDA's conclusions if it knows it is impervious to political pressure. I urge us to resist the temptation to interfere in this instance, and instead for Congress to allow the dedicated public health professionals at the FDA to do their jobs, continue their investigation, and take any actions that might be needed to protect and promote women's health.

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[2] 21 CFR 208 "Medication Guides for Prescription Drug Products"

Mr. SOUDER. Dr. Harrison.

STATEMENT OF DONNA J. HARRISON, M.D., MEMBER, MIFEPREX SUBCOMMITTEE OF AMERICAN ASSOCIATION OF PROLIFE OBSTETRICIANS AND GYNECOLOGISTS

Dr. HARRISON. Chairman Souder, Mr. Waxman, Ranking Member Cummings, and distinguished members of the committee, I present my testimony based on my observations and research as a board-certified obstetrician-gynecologist who has personally examined 850 of the 950 adverse event cases reported to the FDA after RU–486 abortions and also based on data from the CDC presented at the CDC workshop in Atlanta last week, which I attended.

The FDA outlined areas of consideration prior to withdrawing approval of RU–486 and these are as follows: Examining the evidence that RU–486 caused the adverse events; how soon these events occurred after RU–486; how severe these events are; can these adverse events be predicted or avoided; and how safe is the alternative treatment, surgical abortion?

I will speak first about the five Clostridium Sordellii deaths. At the CDC-FDA workshop in Atlanta last week, Drs. Sternberg, Miech, and McGregor detailed the evidence that RU–486 interferes with the body's ability to fight infection by blocking glucocorticoid receptors in the immune system. One of the many studies demonstrated that mice injected with a certain bacterial product die at a rate of 13 percent, but when these mice are given even tiny doses of RU–486, 100 percent of the mice die. The five women who died from infection with C. Sordellii during their RU–486 abortions tragically illustrate the same concept, as illustrated by data from the CDC presented by Drs. Fischer and McGregor.

The statement has been made by some spokespeople from the FDA that the C. Sordellii deaths may be due to a change in the bacteria itself. This question was specifically addressed and specifically refuted by CDC data presented by Dr. McDonald. Some FDA spokespeople have implied that there are comparable numbers of deaths from C. Sordellii in term pregnancy. This is epidemiological nonsense. Dr. Fischer reported CDC data which revealed 5 deaths from C. Sordellii in 550,000 RU–486 abortions. Dr. Fischer reported 8 deaths from C. Sordellii in 30 years out of well over 70 million deliveries. The risk of death from C. Sordellii with RU–486 is well over 50 times greater.

Dr. Fischer reported no deaths from C. Sordellii in 30 years of surgical abortion data. Dr. Greene reported 25 deaths from other causes of infections in 13,161,608 surgical abortions. The risk of death from Clostridium Sordellii with RU–486 is 10 times greater than the risk of death from all other kinds of infections in surgical abortion. Dr. Greene from Harvard recently published this data. Remember also that the women who died during their RU–486 abortions were all healthy. They had no risk factors predisposing them to death, especially from a bacteria that rarely causes death in humans with a normal immune system. The CDC-FDA panelists were unable to identify any risk factors to predict who is more likely to die from C. Sordellii infection, nor could they identify any treatment that would save a woman once she was diagnosed with C. Sordellii infection. C. Sordellii infection during an RU–486 abortion is 100 percent fatal, despite any and all treatment. These deaths are completely preventable.

But septic deaths are not the only health hazard posed by RU–486 abortions. At least 116 women have been transfused from massive bleeding, and at least 54 of them lost over one-half of their blood volume. The medical literature states that 1 to 2 out of every 1,000 women will need to be transfused for massive hemorrhage. Studies that compared surgical and RU–486 abortions show much higher rates of blood loss in RU–486 abortions. These are detailed in my written testimony. And there is no way to predict who will hemorrhage.

The hazards to women's health from just the infections and hemorrhages alone due to RU–486 clearly constitute ample cause for the FDA to withdraw approval from RU–486. Thank you.

Mr. SOUDER. Thank you.

[The prepared statement of Dr. Harrison follows:]

STATEMENT BY

DONNA J. HARRISON, M.D.

BEFORE THE
HOUSE COMMITTEE ON GOVERNMENT REFORM, SUBCOMMITTEE ON
CRIMINAL JUSTICE, DRUG POLICY AND HUMAN RESOURCES

ON

RU-486: DEMONSTRATING A LOW STANDARD FOR WOMEN'S HEALTH

May 15, 2006

Chairman Souder, Ranking Member Cummings, distinguished members of the Committee, thank you for inviting me here today to discuss the safety of RU-486 ("mifepristone") abortions. The conclusions I will present rest on my observations as a board certified obstetrician-gynecologist who has examined 850 RU-486 adverse even reports ("AERs") filed with the Food and Drug Administration ("FDA").[1]

In a letter submitted by the Food and Drug Administration ("FDA") to Chairman Souder,[2] FDA described the criteria it would use in determining whether a drug should be removed from the U.S. market. They were as follows:

> The decision to withdraw a drug from marketing, or to withdraw the approval of a drug, is a complex decision that is based on a number of important considerations, of which potential causality is only one. Other important considerations include the severity and nature of the adverse event in question, the incidence of the event in relation to drug use, the ability to modify or predict the potential for the adverse event, and the availability of alternative treatments and their relative safety.

I wish to address each of these as they relate to both the septic deaths and hemorrhages outlined in the Adverse Event Reports. I will consider first the septic deaths in light of the Centers for Disease Control and Prevention ("CDC")-FDA Workshop on "Emerging Clostridial Disease" that was held last week in Atlanta.

1. Research presentations supported a causal association between mifepristone immune suppression and death from *Clostridial* sepsis.

The presentations of Dr. Esther Sternberg, Dr. Ralph Miech, and Dr. James McGregor indicate that it is plausible that mifepristone ("RU486") impairs the innate immune system. This impairment in turn leads to the host's inability to fight off infection from *Clostridial* bacteria which would otherwise not cause severe illness in humans. Sternberg and others addressed the ability of mifepristone to block innate immune response, and detailed the molecular mechanism by which this blockade takes place. Sternberg reported on her work with blockade of glucocorticoid receptors in sepsis. Mifepristone was able to effectively block immune response in animal models of sepsis, increasing the mortality rate from 13% to 100% in animals that had received mifepristone.[3]

The human experience with immune suppression of mifepristone has been illustrated by the death of 5 U.S. and Canadian women within the 5 years after approval of mifepristone. These deaths were all caused by *Clostridial* organisms which are common in soil, but do not usually infect human beings. However, when the normal human response to *Clostridia sordellii* is impaired, this bacteria causes rapidly fatal infections. Mifepristone blocks human immune response through its effect on glucocorticoid receptors. This should not be completely surprising because mifepristone was originally developed as a medication to block glucocorticoid receptors. Its use as an abortifacient was conceived later. Presentations by Sternberg, Miech, and McGregor linked the molecular mechanism of action of *Clostridial* toxins on a vital cell signaling protein and illustrated the effects of mifepristone blockade on the innate immune system's ability to fight off *Clostridial* infections.

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[1] *See* Margaret M. Gary, M.D., and Donna J. Harrison, M.D., "Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient," *Annals of Pharmacotherapy* (published online Dec. 27, 2005) (www.theannals.com) ("Gary-Harrison article").

[2] Letter, David Boyer, Assistant Commissioner for Legislation, FDA, to Chairman Mark Souder, Subcommittee on Criminal Justice, Drug Policy and Human Resources, House Committee on Government Reform (May 2, 2006)("Boyer Letter").

[3] Sternberg, E. Proceedings of the National Academy Sciences 1989, 86: 2374-2378.

By describing the mechanism of action of mifepristone at the molecular level, a potential causal association between mifepristone use and *Clostridium sordellii* infection and death was clearly shown. Thus, ample evidence was presented in Atlanta to conclude that it is likely - not merely plausible - that mifepristone inhibits the body's immune system leading to infections by bacteria like *C. sordellii* which normally do not cause infections in humans.

2. Death is the most severe type of Adverse Event.

Five otherwise healthy American women and 1 Canadian woman, with no risk factors for rare infection, died with overwhelming *Clostridial* sepsis occurring within seven days of ingestion of mifepristone.

3. Mifepristone use occurred only 1 week before the deaths of the five U.S. women.

These five U.S. and Canadian women had no known risk factors for *Clostridial* sepsis. Recent mifepristone use was the common denominator in their deaths. The sudden nature of the death from *Clostridial* sepsis and the rarity of this type of death in women who have not been exposed to mifepristone indicates strongly that mifepristone is a causal agent in these deaths.

4. Death from *Clostridial* sepsis after mifepristone use is unpredictable; there are no clear predisposing factors which would allow us to identify future victims. Consequently, we are unable to modify or predict a person's potential for these infections.

The Atlanta FDA-CDC meeting made clear that the *C. sordellii* sepsis deaths occurred suddenly without warning. The patients had no known predisposing risk factors. The sudden and unpredictable nature of these events makes it unlikely that such deaths can be prevented. This lack of predictability makes it imperative for the FDA to withdraw marketing approval of mifepristone from the U.S. market until studies can be conducted that identify predisposing risk factors.

5. Mifepristone has been shown to have 10 times more risk of death from infection than its alternative, surgical abortion.

An evaluation of relative risk of death from *C. sordellii* sepsis after mifepristone abortion involves a comparison with the alternative treatment of surgical abortion at less than 8 weeks gestation. (Comparison is also made with childbirth and spontaneous abortion).

Risk of Death from Sepsis after Mifepristone Abortion

As discussed in the article by Fischer of the CDC.[4] The risk of death from infection after mifepristone abortion is estimated as at least 4/460,000. (With the recent death also from *Clostridial* sepsis, we now have at least 5/550,000). Thus the risk of death from *Clostridial* infection during a mifepristone abortion is approximately 1/100,000, which is at least ten times the risk of death from all types of infection after surgical abortion.

This estimate of risk is a minimum possible estimate, biased toward lower risk by the method of calculating the denominator.

Denominator calculation: "Since its approval, there have been an estimated 460,000 uses of mifepristone plus misoprostol in the United States. It is not clear how many women this estimate represents."[5] The denominator is "calculated" from the sales records of the manufacturer, not from actual patient tracking. "There is some uncertainty about this number because, although the manufacturer knows how many tablets it has shipped, it is not absolutely certain how many procedures have been performed with those tablets."[6] Thus, "460,000" is the highest possible number of abortions that could have been performed with mifepristone up to the date of the Fischer article. This number of "460,000" by the date of the Fischer article assumed that each of the packets of mifepristone (which contain three 200mg tablets) sold by the manufacturer, minus an estimate of 10% stocking, represented 3 abortions. This calculation of 460,000 requires that all abortions were performed using the off-label regimen of 200mg of mifepristone.

Risk of death from C. sordellii infections after surgical abortion at less than 8 weeks gestation: It is noteworthy that Fischer reported no deaths from *C. sordellii* after surgical abortion in his retrospective review of *C. sordellii* infections from 1977 to 2001, which he presented at the recent FDA/CDC meeting. In 10 years of surgical abortion data, from 1988-1997 there were no deaths from *C. sordellii* reported after 13,161,608 surgical abortions.[7] Thus in examining deaths from any kind of infection (not *C. sordellii*), Fischer reported only 25 deaths from any kind of infection reported in 13,161,608 surgical abortions at any point in gestation during the 10 years from 1988-1997.

However, as Greene noted, the appropriate comparison is with surgical abortion at less than 8 weeks gestation. Greene reported a rate of death from infection by all causes (not *C. sordellii*) of 0.1 per 100,000 surgical abortions performed at 8 wks gestation or less.[8] This is at least a 10 fold increased risk of death from *Clostridial* infection after mifepristone compared to surgical abortion.

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[4] Fischer, M., MD, et al. "Fatal Toxic Shock Syndrome Associated with Clostridium sordellii after Medical Abortion" NEJM 2005; 353: 2352-60 ("Fischer et al.") p. 2358.

[5] Fischer *et al* p.2358.

[6] Greene, MF, MD, " Fatal Infections Associated with Mifepristone-Induced Abortion" NEJM353; 22 Dec 1, 2005.

[7] Fischer *et al* p 2358.

[8] Greene, MF, MD, " Fatal Infections Associated with Mifepristone-Induced Abortion" NEJM353; 22 Dec 1, 2005

Risk of death from *C. sordellii* infections in childbirth: Dr. Fischer presented a retrospective review of *C. sordellii* infections in pregnancy from 1977 to 2001.[9] He found 8 cases after childbirth. From Fischer's paper the number of births from 1991 to 1999 were 35,701,875.[10] Even if we assume that all 8 cases of *C. sordellii* after childbirth occurred from 1991 to 1999, that gives a rate of 8/35,701,875 or 0.0224 deaths from *C. sordellii* after childbirth. Comparing death from *C. sordellii* after mifepristone abortion to death from *C. sordellii* after childbirth gives fifty-fold (1/0.02) increased risk of death from *C. sordellii* during a mifepristone abortion process compared with the risk of death from *C. sordellii* after delivery.

Risk of death from *C sordellii* infections in spontaneous abortion: Fischer reported 37 infection related deaths after 9,279,100 spontaneous abortions at less than 20 weeks gestation from 1981-1991.[11] This gives a rate of infections from all causes (not *C. sordellii*) of 37/9279100 or 0.4 per 100,000. Note, however, that the appropriate comparison is for *C. sordellii* related deaths in spontaneous abortions at less that 8 weeks gestation. It is of note that Fischer reported no such deaths from *C. sordellii* in spontaneous abortions at the FDA/CDC meeting.

Analysis

In sum, a comparison of the relative safety of alternative treatments reveals that mifepristone carries the higher risk of infection. This is especially true when considering infection with *Clostridia* than does surgical abortion or childbearing. Consideration of the *C. sordellii* sepsis fatalities alone provides ample reason for withdrawing the FDA approval of mifepristone on the basis of the significant risk to American women.

Other Mifepristone Serious Adverse Events

Non-fatal Infections: Mifepristone's risk to the health of American women does not end with infection related deaths. Life threatening infections involving extended ICU hospitalizations were documented in 4 additional women. An additional 43 patients experienced severe pelvic infections, of which the usual sequelae of serious pelvic infection (increased risk of ectopic pregnancy, increased risk of tubal occlusion with subsequent sterility, and increased risk of chronic pelvic pain from adhesive disease) can be expected.

Hemorrhage: Perhaps the most sobering of the AERs are those documenting massive hemorrhage.[12] FDA reports that 116 women have required transfusions for massive bleeding. These cases of massive hemorrhage account for 12% of the AERs filed with the FDA.

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[9] Fischer, M, MD, MPH. Presentation at "Emerging Clostridial Disease Workshop," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Transcript to be available within 30 days of workshop date at http://www.fda.gov/cder/meeting/clostridia_disease.htm

[10] Fischer *et al* p. 2358.

[11] Fischer *et al* p. 2358.

[12] Boyer Letter at 8.

In our review of the AERs filed with FDA from September 2000 – September 2004[13] combined with our yet unpublished data from September 2004 – July 2005, we found 15 cases of massive hemorrhage, where women lost more than half of their entire blood volume (requiring 4 or more units of PRBC's to stabilize). These women would have died without rapid access to emergency room services.[14]

Also in the Gary-Harrison review to July 2005, 18 of the 91 cases of transfusions documented (20%) did not even record the amount of blood transfused. Therefore, one-fifth of these AERs, some involving clinical descriptions that would have indicated the need for large amounts of blood, did not include the amount of blood transfused. This prevented them from being tallied as "life-threatening" in our analysis of mifepristone hemorrhage cases.

Using the criteria FDA presented to Chairman Souder in its letter dated May 2, 2006, I will now analyze the mifepristone bleeding cases. Bear in mind that in the United States physicians are not required to report adverse events to either the FDA or the drug manufacturer. Consequently, the FDA estimates that it receives adverse event reports for only 1-10% of drug complications.

Mifepristone abortions can cause massive hemorrhage: FDA's mifepristone AER reports document at least 116 women who have required transfusions due to massive blood loss while undergoing mifepristone abortions. There is no doubt that the blood loss took place while each patient after mifepristone use. At least 15 women (as of July 2005) lost over half of there blood volume. Hemorrhage sufficient to require transfusion is a severe adverse event reported in 12% of the AER's filed with FDA. Life-threatening hemorrhage was documented in at least 1.6% of the AER's filed with FDA. In my experience as an ob-gyn, the volume of blood loss seen in the life-threatening cases is comparable to that observed in major surgical trauma cases like motor-vehicle accidents. This volume of blood loss is rarely seen in early surgical abortion without perforation of the uterus, and it is rarely seen in spontaneous abortions.

The massive hemorrhage seen during mifepristone abortions is sporadic and unpredictable: No risk factors for massive hemorrhage have been identified, and this unpredictability in life-threatening hemorrhage increases the risk to women, especially women who may not have immediate access to medical services capable of transfusion.

The risk of bleeding from mifepristone abortions is much greater that the risk of hemorrhage from surgical abortion: Paul estimates 130 transfusions per 100,000 uses at 63 days gestation or fewer for mifepristone abortions – about 1.3 per thousand.[15] To date, FDA reports 116 patients requiring transfusions out of an estimated 550,000 uses, which gives a transfusion rate of at least 21 women per 100,000 uses – but, as noted above, AER underreporting is highly likely. The FDA reports at least confirm the general level of hemorrhage seen by Paul.

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[13] Gary Harrison article.

[14] The use of mifepristone in rural areas of the underdeveloped world in which there is no access to medical facilities capable of providing transfusions using a safe blood supply must be strongly discouraged.

[15] Maureen Paul *et al.*, eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999) ("*A Clinician's Guide*"): at 202.

Unfortunately, reliable data on transfusion rates for surgical abortion in the United States are not available. This underlines the need, as expressed by the CDC, for accurate morbidity data on surgical abortion. That being said, Jensen compared outcomes of surgical and mifepristone abortion patients in some subjects of the single American clinical trial.[16] In the women who required surgery after receiving mifepristone, 12.5% underwent emergency surgery for acute bleeding. *No* women in the surgical group required emergency surgery for acute bleeding.

The ACOG Practice Bulletin on Medical Management of Abortion reports a rate of slightly less than 1% of women will need emergency curettage for bleeding.[17] Kruse, in a review of complications from mifepristone abortions, observes:[18]

> "The reported frequencies of intervention for hemorrhage have been somewhat higher in very large series of mifepristone abortion. Aubeny *et al.* reported that 0.9% of 1029 women in a multicenter trial with mifepristone and misoprostol required hemostatic procedures. Similarly 0.4% of participants in multicenter trials with 200 mg mifepristone followed by 800mg misoprostol intravaginally required emergency curettage; in one of these trials 0.2% of women received transfusions. Spitz *et al.* reported that 56 (2.6%) of 2121 women who received 600mg of mifepristone and 400 ug misoprostol orally through 63 days gestation required suction curettage for excessive bleeding, and 4 (0.2%) received transfusions. Importantly, the risk of curettage, hospitalization, or intravenous flid administration was 2 times greater (4% vs 2%) for women at > 49 days gestation than among those at < or = 49 days gestation. Winikoff *et al.* reported that 3 (0.2%) of 1373 subjects in developing countries who received mifepristone and misoprostol required transfusion. Peyron *et al.* found no clinically significant decrease in hemoglobin levels among 878 women who received mifepristone and misoprostol; however, 1 subject (0.1%) did have a decrease from 13.0g/dL to 6.1g/dL necessitating emergency curettage and a blood transfusion. In the largest multicenter trial ever published with mifepristone, Ulmann et al reported that 0.8%of the 15,709 women required emergency curettage and 11 (0.1%) received transfusions.

Publishing on the experience in China with mifepristone abortions, Wu states:

> The main side effect was prolonged bleeding, about 14-16 days, in women with complete abortions. This is significantly longer than the 7 to 9 days of bleeding after surgical abortion. The common complications of medical abortion are

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[16] Jensen, J.T. *et al.*, "Outcomes of Suction Curettage and Mifepristone Abortion in the United States," *Contraception* (1999): 153-159.

[17] ACOG Practice Bulletin No 26, April 2001, p 6.

[18] Kruse, B. *et al.*, "Management of Side Effects and Complications in Medical Abortion" American Journal of Obstetrics and Gynecology (Vol 183, No 2 Aug 2000): S65-S75 (CITATIONS OMITTED).

> profuse bleeding and allergy. Treatment of profuse bleeding by surgical intervention is simple and effective, and reported rates of emergency curettage were 0.7 to 4% and of blood transfusion, 0.05% to 0.15% in the clinical trials.[19]

Thus, a number of large studies conducted in diverse locations around the world demonstrate a rate of hemorrhage requiring transfusion of between 0.1% to 0.2%. This means that there will be at the very least, between 100 and 200 transfusions for every 100,000 mifepristone abortions, which translates into at least 500 to 1000 American women who would have needed blood transfusions to date because of massive hemorrhage from mifepristone abortions.

Conclusion

The danger of post-mifepristone massive blood loss requiring transfusions would in and of itself would require withdrawal of marketing approval. This danger and the risk of fatal infections provide FDA with ample reason to stop the use of mifepristone. If the distributor will not voluntarily remove this drug from the market, then FDA must act to protect the health and safety of American women.

Respectfully submitted,

Donna J. Harrison, M.D.
Chairman, Subcommittee on mifepristone
American Association of Prolife Obstetricians and Gynecologists

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[19] Wu, Shangchun, "Medical Abortion in China" *JAMWA* (v. 55: no. 3)(Supplement 2000): 197-199, 198.

	Number of Adverse Events		Sept 2000 to July 2005	
	Sept 2000-Sept 2004	Sept 2004- July 2005		09/00-3/31/06
elapsed months				65 months (#/mo)
Adverse Event Totals				1024 AERs (16/mo)
Total cases	607	250	857	950
Deaths	5	3	8	
Life Threatening Events (CTCAE 4)	64	18		
Severe Adverse Events (CTCAE 3)	224	105		
Types of Adverse Events				
Hemorrhagic Events Total	237 (36%)	100 (40%)	337 (39%)	
Hemorrhage Deaths (CTCAE 5)	1			
Life threatening Hemorrhage (CTCAE4)	42	12		
Severe Hemorrhage (CTCAE 3)	168	81		
Infectious Events Total	66 (10%)	34 (13.6%)	100 (12%)	9.3%**
Infection Deaths (CTCAE 5)	2	3		
Life Threatening Infections (CTCAE 4)	4	3		
Severe Infections (CTCAE3)		23		
Ectopic Pregnancies				
Death from Ruptured Ectopic (CTCAE 5)	1			
Life Threatening Rupture (CTCAE 4)	10	3		
Serious:Emergency Surgery (CTCAE 3)	7	1		
Transfusions	68 (11%)	17 (7%)*	85 (10%)*	116 (12%)

* Excludes cases where transfusion indicated but not specifically documented

**Excludes cases of STI's and toxic shock.

FDA criteria for inclusion in the category of "Severe Infection" does not match CTCAE criteria for severe or life threatening infections.

FDA Criteria for severe infection
hospitalization for 3 or more days
IV antibiotics for 24 hours or more
Antibiotic useage for 3 days or more
Other findings

CTCAE criteria	(CTCAEv3.p36) Infection with unknown ANC
Grade 3 (Severe)	IV antibiotic, antifungal or antiviral intervention indicated Interventional radiology or operative intervention indicate
Grade 4 (Life- threatening)	Life threatening consequences: septic shock hypotension acidosis necrosis

FDA Letter to Souder

04/17/02 to 03/31/06	11/12/04 to 03/31/06	07/19/05 to 03/31/06
48 months	17 months	9 months
941AERs (20/mo)	320 AERs (19/mo)	111 AERs (12/mo)

RESEARCH REPORTS

Women's Health

Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient

Margaret M Gary and Donna J Harrison

BACKGROUND: The systematic analysis of morbidity and mortality for the Food and Drug Administration (FDA)–approved medical abortion regimen using mifepristone is possible using data from the FDA's Adverse Event Reporting System.

OBJECTIVE: To assess mifepristone's mortality, morbidity, sentinel events, and quality of postmarketing surveillance using mifepristone adverse event reports (AERs).

METHODS: Six hundred seven unique mifepristone AERs submitted to the FDA over a 4 year span were coded using the National Cancer Institute's Common Terminology Criteria for Adverse Events. Coding was based only on data in AERs and may underestimate severity and treatment rendered. Two board-certified obstetrician/gynecologists, the authors, made individual evaluations, compared them, and agreed upon final coding.

RESULTS: The most frequent AERs were hemorrhage (n = 237) and infection (66). Hemorrhages included 1 fatal, 42 life threatening, and 168 serious cases; 68 required transfusions. Infections included 7 cases of septic shock (3 fatal, 4 life threatening) and 43 cases requiring parenteral antibiotics. Surgical interventions were required in 513 cases (235 emergent, 278 nonemergent). Emergent cases included 17 ectopic pregnancies (11 ruptured). Second trimester viability was documented in 22 cases (9 lost to follow-up, 13 documented fetal outcome). Of the 13 documented cases, 9 were terminated without comment on fetal morphology, 1 was enrolled in fetal registry, and 3 fetuses were diagnosed with serious malformations, suggesting a malformation rate of 23%.

CONCLUSIONS: Hemorrhage and infection are the leading causes of mifepristone-related morbidity and mortality. AERs relied upon by the FDA to monitor mifepristone's postmarketing safety are grossly deficient due to extremely poor quality.

KEY WORDS: adverse event reporting system (AERS), medical abortion, Mifeprex, mifepristone, mifepristone adverse events, mifepristone-induced septic shock (MISS), RU486.

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Since the Food and Drug Administration (FDA) approved mifepristone in September 2000, safety concerns have mounted; the FDA's July 2005 press release[1] announcing 2 additional deaths underscored these worries. To date, the FDA has not publicly described mifepristone's non-fatal sequelae as discovered through adverse event reports (AERs). This study systematically analyzes mifepristone AERs submitted between September 2000 and September 2004, using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3; Table 1).[2] CTCAE coding allows for data analysis by providing uniform numerical grading of event severity across different diagnoses.

Methods

The FDA released 637 mifepristone AERs documenting 607 unique events pursuant to a Freedom of Information Act request. All identifiers for patient, practitioner, or facility were removed from the AERs. Mifepristone's distributor submitted 592 of the 637 AERs; the rest were filed from various sources including foreign health authorities, Pharmacia, and others.

The vast majority of mifepristone AERs submitted to the FDA by the drug sponsor lacked critical information needed for complete case assessment.[3-10] Analysis and coding were based only on the contents of the AER. Even if the facts presented in the AER strongly suggested a stan-

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Author information provided at the end of the text.

dard course of treatment (eg, transfusion), that treatment was deemed not to have taken place unless there was explicit documentation. Consequently, poor AER documentation almost certainly resulted in the underestimation of the severity of some adverse events.

An absolute rate of mifepristone abortion complications in the US cannot be determined from the FDA's AERs because these voluntary and sporadically submitted reports provide neither an accurate numerator (number of adverse US events) nor an accurate denominator (number of US mifepristone abortions). However, the data allow some estimation of the types, severity, and percent frequency of reported events. Sentinel events requiring further investigation were also recognizable.

Results

The most frequent serious (CTCAE 3) and life-threatening (CTCAE 4) adverse events were hemorrhage (210 pts.), infection (46 pts.), and missed diagnosis of ectopic pregnancy (17 pts.). Table 2 contains the number of AERs by age and CTCAE grade. Five deaths (CTCAE 5) were reported,[11-15] including one 16-year-old,[11] along with 64 life-threatening events (CTCAE 4) and 224 serious events (CTCAE 3). The distribution of cases per CTCAE grade by age was roughly proportional except for deaths. The single death occurring in the 13–17 year age category represented 20% of the deaths, whereas this age group presented only 2% of all AERs (13 of 607).

Table 3 classifies AERs by CTCAE grade and diagnosis, including information on the group aged 13–17 years. Because the pediatric age encompasses a time of physical maturation, much of which is hormonally mediated, special scrutiny of this population is warranted. Both the US and French trial data specifically excluded women under 18 years of age; thus, the adverse events analyzed here present uncommon public information available on mifepristone's clinical use in the 13–17 year age range.

Table 1. Common Terminology for Coding Adverse Events[2]

Grade	Severity of Adverse Event(s)
1	mild
2	moderate
3	severe
4	life threatening or disabling
5	death related to adverse event(s)

The 607 AERs included 5 deaths: 2 Californians, from sepsis[13,14]; a Tennessee woman with a ruptured ectopic pregnancy[12]; a Swedish teen, from massive hemorrhage[11]; and a British female, from "unknown etiology."[15] This last patient presented to the emergency department in shock and was found on autopsy to have 1 liter of blood in her stomach and 2 gastric ulcers. Sepsis is a known risk factor for stress-related gastrointestinal bleeding[16]; thus, sepsis is a plausible etiology for shock in this patient. Three deaths were not documented in these AERs: a participant in Canadian trials, from sepsis; an Asian Californian, from sepsis (December 2003); and a white Californian, from sepsis (June 2005). The FDA recently announced findings from the Centers for Disease Control and Prevention that all 5 of the sepsis deaths (4 Americans, 1 Canadian) have been linked to *Clostridium sordellii*.[17] Thus, there has been a total of 8 known deaths to date, including 5 Americans.

The severity of hemorrhage was coded based on the patient's pretransfusion hemoglobin level, the number of units transfused, the location and nature of surgical intervention, and the clinical description of the event according to the guidelines for CTCAE coding of hemorrhagic adverse events. However, in the majority of the AERs reporting hemorrhage, critical information (eg, baseline blood counts, vital signs, number of units transfused, posttransfusion hemoglobin or hematocrit level) was absent. Forty-two women experienced a life-threatening hemorrhage, as defined by active hemorrhaging with hemoglobin less than 7 g/dL and the transfusion of 2 or more units of packed red blood cells (PRBCs). One hundred sixty-eight women had severe hemorrhage, defined by hemoglobin of 7 g/dL or above and transfusion. Overall, 39% of AERs reported hemorrhage.

Serious or life-threatening infections were reported for at least 46 women, of whom 2 were aged 13–17 years.[18-20] Four women who had life-threatening infections but survived were in septic shock at the time of presentation to the emergency department.[18,19,21,22] One patient (aged 15 y) pre-

Table 2. CTCAE Grade and Patient Age of Mifepristone Adverse Events[a]

	Grade 5 (N = 5)	Grade 4 (N = 64)	Grade 3 (N = 224)	Grade 2 (N = 344)	Grade 1 (N = 4)	Uncodable (N = 11)
Age (y)	Pts., n (%)	Pts., n (%)	Pts., n (%)	Pts., n (%)	Pts., n (%)	Pts., n (%)
13–17	1 (20)	3 (4.7)	4 (1.8)	8 (2.3)	0	0
18–35	2 (40)	46 (71.8)	172 (76.8)	281 (81.7)	2 (50)	9 (82)
36–46	1 (20)	12 (18.8)	42 (18.7)	36 (10.5)	2 (50)	0
Undocumented	1 (20)	3 (4.7)	6 (2.7)	19 (5.5)	0	2 (18)
TOTAL	5 (100)	64 (100)	224 (100)	344 (100)	4 (100)	11 (100)

CTCAE = Common Terminology Criteria for Adverse Events.

[a] Adverse events reported are greater than number of enrolled patients since some patients experienced more than one adverse event.

sented with adult respiratory distress syndrome (ARDS) from sepsis.[18] A second patient presented with ARDS from *Escherichia coli* sepsis.[21] A third presented with toxic shock syndrome.[22] A fourth (aged 16 y) presented with group B Streptococcus septicemia.[19] In addition to these 4 patients with documented infectious etiology, a fifth patient presented with disseminated intravascular coagulopathy (DIC) with hepatic and renal failure.[23] Her AER exhibited poor documentation, including only information on outpatient treatment for bacterial vaginosis. Because there was no documentation of infection, she was not included in the CTCAE 4 category for infection, although it is probable that the DIC was infectious in origin. Forty-three additional women required parenteral antibiotics for severe pelvic infection, and an additional 14 were treated for pelvic infections as outpatients. Overall, 11% of AERs reported an infectious complication

The third most common class of severe adverse events was undiagnosed ectopic pregnancy. Seventeen patients had ectopic pregnancies that were undetected at the time of mifepristone administration. Eleven of these were ruptured at the time of diagnosis[12,24-33] (CTCAE genitourinary grade 4), including one death (CTCAE 5).[12] Three of the 17 were cornual pregnancies,[31,33,34] and one was a cervical pregnancy that resulted in a hysterectomy in a 29-year-old patient.[35] Overall, 2.8% of AERs reported unrecognized ectopic pregnancy.

Seven additional diagnoses of possible sentinel events were (1) myocardial infarction in a previously healthy 21-year-old woman,[36] (2) prolongation of QT interval on electrocardiogram in another woman,[37] (3) pulmonary embolism,[38] (4) exacerbation of Crohn's disease,[39] (5) precipitation of a sickle cell crisis,[40] (6) acute pancreatitis,[41] and (7) drug interaction resulting in liver failure in an HIV-positive patient.[42]

One unexpected finding was a number of allergic reactions ranging from hives to severe generalized urticaria. One patient was hospitalized for 4 days and treated with intravenous diphenhydramine and oral prednisone.[43] Eight patients were treated as outpatients, and 4 required no treatment.

The extent of treatment required to manage the adverse events is presented in Table 4. Sixty-eight women received transfusions. Nineteen (28%) of these required 3 or more units of PRBCs. In 15% of cases with transfusion, the number of units was not documented in the AER. At least 513 surgical procedures were performed in the 607 patients with adverse events. When a patient had more than one surgery performed, only the most extensive surgery was included in the tabulation. (For example, if a patient had a dilatation and curettage and then a subsequent laparotomy, only the laparotomy was included. For patients with more than one dilatation and curettage, only one was included in the tabulation.) There were 235 emergency surgeries performed. Of these, 17 (7%) were emergency laparotomies: 16 were for ectopic pregnancies (1 ectopic pregnancy was managed laparoscopically) and one laparotomy was for sepsis. Two of the 5 deaths were intraoperative. The remaining 93% of emergency surgeries were emergency dilatation and curettage procedures performed to arrest hemorrhage. At least 40% of the patients were hospitalized for treatment, including 12 admissions to the intensive care unit. Fifty-seven percent were managed as outpatients and, in 3%, the site of treatment was not documented.

Because mifepristone abortions result in exposure of the fetus to known teratogens, the AERs were analyzed for information on fetal outcome after exposure, where documented (Table 5). Of the 278 pregnancies terminated after mifepristone failure without other diagnoses, 58 (21%) had documented fetal viability by ultrasound on return visit,

Table 3. CTCAE Grade and Diagnosis

	Hemorrhage		Infection		Genitourinary		Other		Total	
CTCAE Grade	All Pts. (n)	Adolescents (n)	All Pts. (n)	Adolescents (n)	All Pts. (n)	Adolescents (n)	All Pts. (n)	Adolescents (n)	All Pts. (n)	Adolescents (n)
5	1	1	3[a]	0	1	0	0	0	5	1
4	42	1	4	2	10	0	9	0	64	3
3	168	3	43	1[b]	7	0	5	0	224	4
2	19	0	14	1	301	6	10	1	344	8
1	0	0	0	0	0	0	4	0	4	0
Uncodable	7[c]	0	2	0	0	0	2[d]	0	11	0
TOTAL	237	5	66	4	319	6	30	1	652	16
% of diagnoses	36		10		49		5			

AERs = adverse event reports; CTCAE = Common Terminology Criteria for Adverse Events.

[a] This includes death of the British woman with clinical picture consistent with sepsis.

[b] Poor documentation precluded accurate coding. Actual event probably a 4 but pertinent lab data not documented on AER.

[c] This includes 2 patients with hemorrhage and infection, 2 patients with some indication of severe hemorrhage (Hb <7.5), and 3 patients with heavy bleeding. All patients in this category lacked critical information, which made coding impossible.

[d] Both are cardiac events that lacked adequate documentation to code.

and 36 (13%) had documented fetal demise or retained products of conception without a fetus. However, 184 (66%) had no documentation of fetal status. Of the 22 fetuses documented to be viable in the second trimester, 9 were lost to follow-up and 13 had a documented outcome to the pregnancy. Of those 13, 9 had a termination of pregnancy with no documentation of fetal morphology, 1 was enrolled in a fetal registry,[44] and 3 had documentation of fetal anomalies: (1) Mobius syndrome,[45] (2) neural tube defect,[46] and (3) oligodactylia, monodactylia, facial dysmorphia, and meningo-encephalocele.[47] (One additional AER[48] referred to a separate fetal report implying malformation. However, that fetal report was not included in the information released and thus not counted in our calculation of malformation rate.) Assuming normal fetal morphology in all 9 pregnancies that were terminated without documenting information about the presence or absence of malformations and assuming normal fetal morphology for the patient enrolled in the fetal registry, the rate of fetal malformations would still be at least 3 (23%) of 13.

Discussion

The pathophysiology of the rapid onset of sepsis following pregnancy terminations with mifepristone and the unusual afebrile and hemoconcentration presentation is still unclear. An interesting theory was recently published linking the rapid onset of sepsis with mifepristone's blockade of glucocorticoid receptors (mifepristone-induced septic shock).[49] Studies investigating the pathophysiology of septic shock have shown a noncompetitive, dose-dependent repression of the glucocorticoid receptor by both *Bacillus anthracis* lethal toxin[50] and the *Clostridium sordellii* lethal toxin.[51] Blockade of glucocorticoid receptors at the endometrial level may allow for ascending infection into a fertile medium of dead fetal tissue surrounded by an endometrium that lacks normal innate immune mechanisms. Further research into glucocorticoid receptor blockade by mifepristone resulting in the loss of the antibacterial role of the innate immune system at the endometrial level should be pursued.

Table 4. Extent of Treatment Interventions

Treatment Interventions	Pts. (%)
Transfusions	68 (100)
≥4 units PRBCs	9 (13)
3 units PRBCs	10 (15)
2 units PRBCs	38 (56)
1 unit PRBCs	1 (1)
units not documented, n	10 (15)
transfusion implied but not documented[a]	1
Surgeries	513 (100)
emergent	235 (46)
emergency laparotomy	17
intraoperative death	2
hysterectomy	1
salpingectomy with or without oophorectomy	7
adnexal surgery unspecified	4
cornual surgery unspecified	3
emergency D&C for hemorrhage	218
nonemergent	
D&C for failures without other indications	278 (54)
Site of Treatment Intervention	607 (100)
hospitalizations	241 (40)
intensive care unit admissions	12
inpatient hospitalizations	130
emergency department outpatient	99
outpatient management	345 (57)
site of treatment not documented	21 (3)

D&C = dilatation and curettage; PRBCs = packed red blood cells.
[a]AER reported that patient said she was given blood.

With mifepristone abortions, the rate of failure to cause complete termination of pregnancy increases dramatically, along with hemorrhagic events, as the gestational age and the size of the placenta increases. The US clinical trial demonstrated a failure rate of 8% at 49 days or less from the last menstrual period (LMP), increasing to 17% at 50–56 days from the LMP, and further increasing to a 23% failure at 57–63 days from the LMP, as established by sonographic criteria.[52] Based on the data from this trial, the FDA approved mifepristone for use as an abortifacient up to 49 days from the LMP, but failed to require sonographic data for the accurate determination of gestational age. Furthermore, clinics nationwide routinely advertise mifepristone's use up to 63 days from the LMP, and, thus, would incur a failure rate of 23% or higher in addition to the inaccuracies of the methods used to date the pregnancies.

One serious concern raised by this review of AERs is the suggested fetal malformation rate of at least 23% following mifepristone failures that resulted in continuation of a live pregnancy. Misoprostol is a known teratogen, but the extent of the teratogenicity of mifepristone has yet to

Table 5. Fetal Outcome After Mifepristone Exposure

Outcome	Pts. (%)
Surgeries—Nonemergent	
D&C for failures without other indications	278 (100)
continuing viable pregnancy	58 (21)
continuing pregnancy with fetal demise	13 (5)
continuing pregnancy with viability unknown	184 (66)
retained products of conception	23 (8)
Fetal outcome after exposure	
second trimester with documented viability	22 (100)
lost to follow-up	9 (41)
known outcome	13 (59)
Known outcome of pregnancy	13 (100)
terminated without documentation of fetal status	9 (69)
documented fetal malformation	3 (23)
enrolled in fetal registry	1 (8)

D&C = dilatation and curettage.

be well documented. Fetal malformations were noted in 3 of the 13 women who had pregnancies with known outcome. Another 9 women continued pregnancies without any documentation in the AERs of the outcome of the fetus. It is clear that a mandatory fetal registry should be established to ascertain the true incidence of fetal malformation in pregnancies that are continued after exposure to mifepristone and misoprostol.

Another serious concern is the number of missed diagnoses of ectopic pregnancies that resulted in rupture. Ectopic pregnancy is an absolute contraindication to the use of mifepristone, and failure to rule out ectopic pregnancy resulted in one death, as well as unnecessary morbidity. Requiring ultrasound documentation of intrauterine location of the pregnancy by a qualified ultrasonographer prior to the administration of mifepristone would reduce this life-threatening complication to a minimum.

The incidence of allergic reactions to mifepristone requires closer examination. Assuming that all patients were exposed to mifepristone for the first time, they could not have mounted an immunoglobulin E–mediated mifepristone allergic response. Inflammatory reactions reported as allergic reaction in the AERs are due to the release of proinflammatory mediators, such as histamine, prostaglandins, leukotrienes, and interleukins, which result in urticaria, rhinitis, conjunctivitis, or asthma. Blockade of cortisol receptors by mifepristone can result in an uncontrolled production and release of an excess of these proinflammatory mediators. Mifepristone's ability to block cortisol receptors has been well documented.[53] These proinflammatory reactions reported as allergic reactions in AERs may be due to the action of mifepristone's blockade of cortisol receptors. This potentially serious adverse effect resulting from mifepristone-induced blockade of cortisol receptors deserves further investigation.

Aside from specific safety issues related to mifepristone, studying these reports has been highly instructive for what they reveal about the FDA's Adverse Event Reporting System for all drugs. Michael F Mangano, principal deputy inspector general of the Department of Health and Human Services, stated in testimony before the US Senate[54]:

> Adverse Event Reporting systems typically detect only a small proportion of events that actually occur. They are passive systems that depend on someone linking an adverse event with the use of a product, then reporting the event Rather the system generates signals that FDA must assess to confirm if, in fact, a public health problem exists.... With limited information to draw upon to generate signals, it is not surprising that FDA rarely reaches the point of knowing whether a safety action is warranted to protect consumers.

If our survey of mifepristone AERs is representative of adverse event reporting for all drugs, the American public should be greatly alarmed. In this instance, a majority of the AERs analyzed do not provide enough information to accurately code the severity of the adverse event in question. The deficiencies were so egregious in some instances as to preclude analysis. It is clear that input quality control is necessary for Medwatch to function; this systemic deficiency clearly impairs the FDA's ability to fully assess mifepristone's safety profile because the necessary signals are not being generated.

Conclusions

The AERs discussed above relate to the use of mifepristone in otherwise healthy young women and document a significant risk of severe, life-threatening, or even lethal adverse events. The most common of these adverse events are hemorrhage, infection, and missed diagnosis of ectopic pregnancies. The most commonly fatal adverse event is sepsis, which may present without fever and progress rapidly to death.

Although neither the manufacturer nor the FDA recognizes a causal link between the use of mifepristone and the adverse events reported, it is undeniable that these women were healthy before the use of mifepristone and became very sick or died shortly after its use. Before any medication is used, a prudent practitioner weighs carefully the risks of the medication with the potential benefits. Medications, such as chemotherapy agents, with life-threatening or potentially lethal adverse effects are acceptable in treating conditions that are themselves debilitating or lethal such as cancer, HIV, sepsis, and others. In these cases, alternative treatments are limited and, without treatment, the disease is rapidly lethal. The use of mifepristone as an abortifacient, however, is radically different. Pregnancy in most instances is a benign, self-limited condition, with duration of approximately 8 months from diagnosis for most women. It generally occurs in otherwise healthy young women. The choice of mifepristone termination over surgical termination is based mainly on patient perceptions of safety, convenience, and privacy, but these perceptions do not accurately reflect the realities of the regimen.

Furthermore, complete, accurate data concerning the public health risk posed by the mifepristone/misoprostol regimen currently in use are not being gathered through the FDA's Adverse Event Reporting System After reviewing over 600 AERs, we believe that the FDA must promptly conduct a thorough review of this aspect of its postmarketing surveillance system to determine whether the failures described above are peculiar to mifepristone reports or are systemic to all drug reports.

Margaret M Gary MD, Obstetrician/Gynecologist, Virginia Beach, VA
Donna J Harrison MD, Chairperson, Subcommittee on Mifeprex, American Association of Prolife Obstetricians and Gynecologists, Eau Claire, MI
Reprints: Dr. Harrison, American Association of Prolife Obstetricians and Gynecologists, PO Box 414, Eau Claire, MI 49111-0414, djharrison@juno.com

Dr. Gary and Dr. Harrison are members of the Subcommittee on Mifeprex of the American Association of Prolife Obstetricians and Gynecologists (AAPLOG), the largest interest group of the American College of Obstetricians and Gynecologists. AAPLOG has filed a Citizen Petition with the Food and Drug Administration requesting withdrawal of approval for mifepristone based on safety considerations.

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EXTRACTO

TRASFONDO: Es posible analizar sistemáticamente la morbilidad y mortalidad del régimen de aborto terapéutico con mifepristona aprobado por la Administración de Alimentos y Drogas (FDA, por sus siglas en inglés) utilizando datos del Sistema de Reporte de Eventos Adversos (AERS, por sus siglas en inglés) de esa agencia.

OBJETIVO: Evaluar la mortalidad, morbilidad, eventos sentinelas, y calidad de la vigilancia posmercadeo utilizando los reportes de eventos adversos con mifepristona.

MÉTODOS: Seiscientos siete reportes de eventos adversos únicos con mifepristona sometidos a FDA durante un período de 4 años fueron codificados utilizando Criterios de Terminología Común para Eventos Adversos del Instituto Nacional del Cáncer (NCI's CTCAEv3, por sus siglas en inglés). La codificación se basó solamente en datos de los reportes de eventos adversos y puede subestimar la severidad y el tratamiento provisto. Los autores, 2 juntas de obstetras/ginecólogos, hicieron evaluaciones de CTCAE, las compararon, y acordaron la codificación final.

RESULTADOS: Reportes de eventos adversos más frecuentes: hemorragia (237) e infección (66). Las hemorragias incluyeron una fatal, 42 potencialmente fatales, y 168 casos serios; 68 requirieron transfusiones. Las infecciones incluyeron 7 casos de choque séptico con 3 casos fatales, 4 potencialmente fatales, y 43 que requirieron antibióticos parenterales. Las intervenciones quirúrgicas totalizaron 513 casos (235 urgencias, 278 no urgencias). Los casos de urgencias incluyeron 17 embarazos ectópicos (11 rupturas). La viabilidad de segundo trimestre fue documentada en 22 casos (9 sin seguimiento, 13 con resultado fetal documentado). De 13 casos documentados 9 terminaron sin comentario sobre morfología fetal, 1 inscrito en el registro fetal, y 3 fetos diagnosticados con defectos del tubo neural que sugieren una razón de malformación de 23% (3 de 13).

CONCLUSIONES: Las principales causas de morbilidad y mortalidad relacionadas con mifepristona son hemorragia e infección. Los reportes de eventos adversos en los que se fundamenta FDA para dar seguimiento a la seguridad posmercadeo de mifepristona son crasamente deficientes debido a su extremadamente pobre calidad.

Ana E Vélez

RÉSUMÉ

INTRODUCTION: Le système américain de pharmacovigilance (Medwatch) permet une analyse systématique de la morbidité et de la mortalité associées à l'utilisation de mifepristone pour induire un avortement

OBJECTIF: Evaluer la mortalité, la morbidité, et l'incidence d'événements sentinelles associés à la mifepristone, de même que la qualité du système de pharmacovigilance américain en utilisant les cas de réactions indésirables rapportées à l'agence américaine des aliments et drogues.

DEVIS EXPÉRIMENTAL: Six cent sept réactions indésirables uniques associées à la mifepristone ont été rapportées à l'agence américaine sur une période de 4 ans. De celles-ci, 592 ont transité par le fabriquant. Chaque réaction a été codifiée en utilisant le dictionnaire terminologique de l'institut national du cancer (National Cancer Institute Common Terminology Criteria for Adverse Events).

RÉSULTATS: En général, les rapports de cas étaient de piètre qualité et beaucoup d'information nécessaire à une codification adéquate manquait. Dans d'autres cas, la codification n'utilisait que les données du rapport de cas et une évaluation par 2 gynécologues obstétriciens diplômés, les auteurs, a révélé une sous-estimation de la sévérité des réactions de même que du lien de causalité. Les réactions indésirables les plus fréquentes incluaient les hémorragies (237) et les infections (66). Parmi les hémorragies, on nota une réaction fatale, 42 ayant mis la vie en danger et 168 cas sérieux. De plus, 68 ont nécessité une ou plusieurs transfusions sanguines. Parmi les infections on a remarqué 7 cas de choc septique dont 3 ayant entraîné le décès et 4 ayant mis la vie de la patiente en danger. De plus, 43 cas ont nécessité l'administration intraveineuse d'antibiotiques. Un total de 513 cas a requis une intervention chirurgicale (235 urgentes, 278 non urgentes). Parmi les chirurgies urgentes on dénombra 17 grossesses ectopiques dont 11 avec rupture de la trompe. La viabilité du fétus jusqu'au second trimestre a été documentée dans 22 cas (9 sans suivi documenté, 13 avec documentation). Des 13 cas documentés, 9 grossesses ont été interrompues sans qu'aucune information sur la morphologie du fétus ne soit documentée, 1 grossesse a été incluse dans un registre médical de suivi de grossesse, et chez 3 fétus, une malformation du tube neural a été observé, suggérant un taux de malformation de 23% (3 sur 13).

CONCLUSIONS: Les hémorragies et les infections sont les causes les plus fréquentes de mortalité et de morbidité associées à l'utilisation de mifepristone pour induire un avortement. Les réactions indésirables rapportées au système de pharmacovigilance de l'agence américaine sont de piètre qualité rendant peu fiable l'évaluation du risque associé à l'utilisation d'un médicament par l'entremise de ce système

Suzanne Laplante

LETTERS AND COMMENTS

AUTHORS' REPLY: First, the Food and Drug Administration's (FDA's) recently published guidance document on adverse events states: "Typical reasons to suspect causality for an event include (1) timing of onset or termination with respect to drug use, (2) plausibility in light of a drug's known pharmacology, (3) occurrence at a frequency above that expected in the treated population, and (4) occurrence of an event typical of drug-induced adverse reactions."[1] Consider these reasons in the fatalities that followed mifepristone use: (1) all of the deaths occurred within 7 days of taking mifepristone, (2) mifepristone-induced suppression of the innate immune system is plausible,[2] and (3) the frequency of fatalities from *Clostridium sordellii* after mifepristone far exceeds the frequency of this infection prior to mifepristone availability. Based on the FDA's guidance, there are multiple reasons to infer a causal link between mifepristone and these deaths.

Second, we believe that pregnancy is in most instances a benign, self-limited condition as evidenced by the statistic cited by Hausknecht: 99 992.9/100 000 women survive pregnancy.

Third, the clinical picture of medically induced abortion can mimic the symptoms of ectopic pregnancy. If these symptoms are incorrectly ascribed to the medical abortion, then delay in diagnosis of the ectopic pregnancy can be lethal. This contraindication to the use of mifepristone has been acknowledged by Danco Laboratories.[3]

Fourth, given the incomplete nature of the Medwatch adverse event report (AER) 3943786-2,[4] we believe our assessment remains plausible. While acetaminophen overdose can be associated with hepatic toxicity, renal failure, and disseminated intravascular coagulation, it is also plausible that this scenario is caused by sepsis with multiorgan failure. Hausknecht infers causality from empty pill bottles but has left out crucial information in his depiction of both the adverse event and its AER. In his letter, he states that the event was related to drug overdose with alcohol. Rather, this AER stated that "current thinking was that this event was related to some sort of drug overdose (Tylenol)" and does not mention alcohol toxicity. One of the cases of fatal mifepristone-associated sepsis syndrome also had no evidence of infection initially, then progressed rapidly to multiorgan failure and death.[5] Hausknecht's assertion that "there are many similar errors of omission and exaggeration" is incorrect. Our review was based on the limited information available in the reports submitted to the FDA by Hausknecht.

Finally, this AER illustrates the lack of documentation provided by Danco. The Medwatch AER 3943786-2 contained no emergency department records, no hospital records, and no white blood cell count or acetaminophen levels.[4] The report appears to reflect an initial conversation between the reporting physician and Danco but the report language is Danco's. It is curious that such an opportunity failed to produce a detailed, clear summary of the hospital course and laboratory findings or even a final diagnosis. It is the ethical responsibility of Danco to seek complete and accurate documentation for these AERs. Failure to do so thwarts postmarketing safety monitoring.

Donna J Harrison MD
Chairperson
Subcommittee on Mifeprex
American Association of Prolife Obstetricians and Gynecologists
PO Box 414
Eau Claire, Michigan 49111-0414
djharrison@juno.com

Margaret M Gary MD
Obstetrician/Gynecologist
Virginia Beach, Virginia

Drs. Gary and Harrison are members of the Subcommittee on Mifeprex of the American Association of Prolife Obstetricians and Gynecologists (AAPLOG), the largest interest group of the American College of Obstetricians and Gynecologists. AAPLOG has filed a Citizen Petition with the Food and Drug Administration requesting withdrawal of approval for mifepristone based on safety considerations.

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Reply: Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient

AUTHORS' REPLY: We thank Shannon for her letter, which corrects our analysis of 1 adverse event report (AER) out of 607. The wording of that report led us to understand that a diagnosis had been made. Reconsidering the wording interpretation, as suggested by Shannon, we agree that this report should probably be classified as "unknown outcome." Inclusion of this case in the "unknown outcome" category, however, does not diminish the concern of the significant potential for fetal malformation in continuing pregnancies after exposure to mifepristone and misoprostol. In fact, as this AER illustrated, there was sufficient concern by Danco Laboratories that it provided information on the ultrasound findings of Mobius syndrome to the patient's obstetrician, but apparently not enough concern to follow up in 7 months to document the outcome of the pregnancy.

The paucity of follow-up information in this AER is another example that demonstrates the inadequacy of AER documentation of fetal exposure to mifepristone. The Food and Drug Administration (FDA) guidance regarding drugs used during pregnancy indicates:

> Regardless of findings from animal studies, we recommend that a pregnancy exposure registry be seriously considered when it is likely that the medicinal product will be used during pregnancy as therapy for a new or chronic condition.[1]

Sirenomelia has been reported after exposure to mifepristone alone in the first trimester.[2] Since, as Shannon writes, an ongoing pregnancy is "an expected event following the use of mifepristone," then a pregnancy registry should have been started at the time of approval. In fact, the FDA states:

> For clinical trials of a medicinal product for use during pregnancy a follow-up study of the pregnancy, fetus and child is important.[3]

Neither the single, nonrandomized, nonblinded, uncontrolled trial used for the initial approval of mifepristone nor the distribution and use of mifepristone by the manufacturer has been characterized by the production of the FDA-recommended follow-up reports, including those for fetal exposure to potential teratogens.

In fact, of the 278 cases of AERs reporting "continuing pregnancy," 184 did not even document whether the fetus was viable. Of the 22 that did document viability into the second trimester, if we include Shannon's case, 10 had no documented follow-up. Of the remaining 12 with some documentation, 9 terminated without any documentation of fetal morphology, 2 had documented malformations, and only 1 was enrolled in a "fetal registry." However, the Organization of Teratogen Information Services has no record of any fetal registries involving mifepristone.[4]

We agree that a "rate of fetal malformations cannot be calculated from the reported 13 cases." In fact, the FDA states, "When risk estimates are calculated, only outcomes from prospectively collected data should be included."[5] It is the manufacturer's ethical responsibility to collect and analyze these data. To fail to collect the necessary data despite clear guidance from the FDA and then claim that there are no reports of fetal anomalies is misleading and raises concerns regarding the sponsor's ethical compulsion.

Margaret M Gary MD

Obstetrician/Gynecologist, Virginia Beach, Virginia

Donna J Harrison MD

Chairperson, Subcommittee on Mifeprex, American Association of Prolife Obstetricians and Gynecologists, Eau Claire, Michigan

Reprints: Dr. Harrison, American Association of Prolife Obstetricians and Gynecologists, PO Box 414, Eau Claire, Michigan 49111-0414, djharrison@juno.com (269)-461-3412 phone

Drs. Gary and Harrison are members of the Subcommittee on Mifeprex of the American Association of Prolife Obstetricians and Gynecologists (AAPLOG), the largest interest group of the American College of Obstetricians and Gynecologists. AAPLOG has filed a Citizen Petition with the Food and Drug Administration requesting withdrawal of mifepristone based on safety considerations.

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Challenges to the FDA Approval of Mifepristone

Byron C Calhoun and Donna J Harrison

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Mifepristone was approved for use as an abortifacient in the US in September 2000, amidst a firestorm of controversy. Efficacious as an abortifacient in combination with misoprostol, current use of mifepristone in the US has resulted in at least 2 deaths in otherwise young healthy women. Significant deviations from the normal Food and Drug Administration (FDA) requirements for drug approval have led to legal challenge. In August 2002, the American Association of Prolife Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America jointly filed a Citizen Petition with the FDA, requesting the FDA to revoke its approval of mifepristone as an abortifacient.[1] The petition cites major deficiencies in the aberrant process that the FDA followed for approving mifepristone, rendering this approval invalid.

Mifepristone Approval Process

Since its discovery in the 1970s by Roussel Uclaf, mifepristone was initially investigated for antiglucocorticoid activities,[2] but was found to have significant activity as an antiprogesterone useful for termination of pregnancies in the first and second trimesters.[3] The contragestive mechanism is primarily due to the effect of mifepristone on the maternal endometrium, not the chorionic villi.[4] This observation leads one to accurately predict the failure of mifepristone to treat ectopic pregnancies. By causing necrosis of the endometrium, mifepristone induces the death of the fetus, but is only weakly effective at inducing subsequent uterine contractility. Therefore, to achieve acceptable clinical efficacy as an abortifacient, mifepristone must be used in combination with a prostaglandin (currently misoprostol) that induces uterine contractility and, thus, evacuation of the products of conception. Mifepristone was approved as an abortifacient in France in April 1990. Ulmann, the developer of mifepristone for Roussel/Hoechst, summarized the history of the introduction of mifepristone to the US[5]:

> In the meantime, President Clinton wrote to Hoechst asking the company to file a New Drug Application (NDA) with the FDA (an unprecedented situation in the pharmaceutical industry!), which Hoechst intransigently refused to do. It also refused our proposal for a new venture, arguing that a start-up company run by former Roussel employees would not protect Roussel and Hoechst from potential problems linked to the product....Finally, the proposed solution was to give the rights (including the manufacturing know-how) to the PC [Population Council], which would be solely responsible for Mifepristone in the United States and would be entitled to take all necessary steps to make it available.

The PC subsequently gave the right to manufacture and distribute mifepristone to a company, newly created solely for this purpose, called Danco. The Population Council/Danco then filed an NDA in 1996. A US trial of the efficacy and safety of the combination of oral mifepristone 600 mg followed 2 days later by oral misoprostol 400 µg,[6] as well as some limited French data on mifepristone, were submitted as part of the NDA for mifepristone.

Aberrance in the FDA Approval Process

ACCEPTANCE OF NONCONTROLLED, NONBLINDED, NONRANDOMIZED STUDIES

The normal FDA approval process requires 2 randomized, blinded, controlled trials to answer questions regarding safety and efficacy of the drug. The use of randomized controlled trials is required by the FDA in its own adminis-

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Author information provided at the end of the text.

Dr Harrison is Chairman, Subcommittee on Mifeprex, American Association of Pro Life Obstetricians and Gynecologists, and coauthor of the Citizen Petition currently before the Food and Drug Administration.

trative laws as the basis for the drug approval process. "Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness."[7] The results of these trials are submitted to the FDA for statistical analysis and a review by the pertinent advisory committee, which then recommends to approve or not approve the drug. Final approval or rejection is made by the pertinent subdivision of the FDA.

However, data submitted to the FDA from the US, as well as data from France, leading to the approval of mifepristone were not gathered from controlled, randomized, or blinded trials. The FDA statistical review highlights this aberrancy: "In the absence of a concurrent control group in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy."[8]

In addition, an FDA investigation of the French data raised concerns about falsification[9]:

> Review of the study records revealed a failure to maintain complete and accurate records; eg, laboratory reports that were missing for 8 of 44 subjects in study 14, and 3 of 52 subjects for study 24. Wrong dates were on lab reports or wrong dates reported for 11 of 44 subjects for study 14. One lab report for each study had the date changed from another existing lab report to make them appear to be separate new reports; missing ultrasound documents for 13 of 44 subjects for study 14 and 7 of 52 subjects for study 24; pages missing from the case record files and unreported aspirations; four ineligible subjects who were entered into study 14; consent forms were dated after the start of study for some subjects, and the investigator had signed consent form sometimes in advance, up to 4 days before the subjects had signed. Other problems included under-reported side effects; eg, a patient bleeding with two subsequent aspirations; convulsions reported as fainting; an expulsion which was actually a surgical evacuation; bleeding, nausea and contractions, or bleeding and pelvic pain.

The FDA promulgates standards for clinical trials as outlined by the International Conference for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.[10] During an FDA investigation of a research site, the discovery of falsification of records can invalidate the data from that site. Approving a drug on the basis of uncontrolled trials with data in violation of ICH Good Clinical Practice guidelines was a clear deviation from FDA standards. Further, since both the US clinical trial data and the suspect French data were obtained from uncontrolled studies, and thus susceptible to significant bias, the scientific merit of such studies is insufficient to warrant approval of any drug, including mifepristone.

INAPPROPRIATE USE OF SUBPART H AS THE LEGAL BASIS FOR APPROVAL OF MIFEPRISTONE

In response to the AIDS crisis, the FDA reconsidered its process for approving drugs intended to treat serious and life-threatening illnesses. This process culminated in 1992 with the adoption of the FDA's Subpart H—Accelerated Approval Regulations[11]:

> This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (eg, ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

Other than mifepristone, the FDA has used this rule only to approve drugs for AIDS, cancer, sepsis, and leprosy.[12,13] Mifepristone was an inappropriate candidate for Subpart H because it neither treats a serious or life-threatening illness nor provides a therapeutic benefit over surgical abortion.

The FDA's improper use of Subpart H appears to have been driven by the agency's concern about the inherent risks of the mifepristone regimen. The FDA approved mifepristone under the restricted distribution provision, 21 CFR §314.520, which allows the agency to impose safety restrictions on drugs approved under its auspices. The FDA, confronted by the Population Council's refusal to establish voluntary restrictions on the use and distribution of mifepristone, viewed Subpart H as the only available regulatory vehicle that might allow for the potential to control some of the dangers of the mifepristone/misoprostol regimen.

FDA SANCTION AND MANDATE OF THE OFF-LABEL USE OF MISOPROSTOL

Ultimately, the FDA based its approval of mifepristone on the combined action of a mifepristone/misoprostol regimen. However, Searle, the manufacturer of misoprostol, did not file a Supplemental NDA for the use of misoprostol as part of an abortion regimen. Since Searle did not pursue approval of misoprostol for use in abortion, the FDA lacked the basis for sanctioning a new indication for misoprostol. Peter Barton Hutt, a former FDA general counsel, commented that the agency's treatment of misoprostol "set an extraordinary precedent" because the FDA was "seemingly encouraging a drug's unapproved use." Hutt also commented that the agency is in an "embarrassing and uncomfortable position."[14] By including misoprostol within the labeling for mifepristone, the FDA mandated the unapproved use of misoprostol as part of the mifepristone abortion regimen,[15] and did this in the face of strenuous objections from the manufacturer of misoprostol.

On August 23, 2000, Searle wrote an open letter to all healthcare practitioners stating that "Cytotec is not approved for the induction of labor or abortion." The letter listed a number of potential "serious adverse events reported following off-label use of Cytotec in pregnant women, including maternal or fetal death."[16] Several key abortion advocates decried Searle's lack of cooperation.[17] The FDA's approval of the mifepristone regimen in the face of Searle's opposition appears to have usurped Searle's rights to control the distribution of its drug.

UNEXPLAINED WAIVER OF THE PEDIATRIC RULE

In the US, the annual number of abortions in adolescents ≤17 years of age is approximately 360 000.[18] Thus, a large number of this population are candidates for mifepristone terminations. The FDA is required to test a drug in the pediatric population if that drug is intended for use in that population.[19] The FDA guidelines for trials in the pediatric population state that the adolescent subgroup should extend from "12 to 16–18 years."[20] The FDA approval letter to the Population Council in September 2000 clearly states this requirement[21]:

> Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred."[19]

Then, inexplicably, the FDA continued in the next sentence of the letter: "We are waiving the pediatric study requirement for this action on this application." When the FDA waives its own rule, it is required that an appropriate explanation of the rationale for the waiver be given along with the waiver. When the FDA adopted the pediatric assessment rule, the agency stated[22]:

> FDA agrees that the burden is on the manufacturer to justify waivers, but believes that the rule already adequately imposes that burden. The rule requires both a certification from the manufacturer that the grounds for waiver have been met and an adequate justification for the waiver request.

No such explanation was provided.

As explained later, the gestational age of a pregnancy must be determined precisely (±1 wk) to minimize the risks of hemorrhage, incomplete abortion, and ongoing pregnancies. Since adolescents are particularly poor historians and often have difficulty allowing a complete pelvic examination, it is particularly frightening that the approved method of pregnancy dating for mifepristone abortion is by patient history and physical examination alone. Since careful follow-up is necessary to confirm completion of mifepristone abortions, it is equally concerning that adolescents are at higher risk of loss to follow-up, especially since these abortions are available without parental notification or consent. Thus, the FDA improperly approved mifepristone for use in pediatric patients without requiring safety and effectiveness testing addressing the special safety concerns of adolescent users.

APPROVED MIFEPRISTONE REGIMEN DOES NOT MIRROR CLINICAL TRIAL CONDITIONS

Data generated from the US clinical trial of mifepristone formed the basis for the FDA's evaluation of the safety of mifepristone in clinical use.[6] But the frequency and types of complications and adverse events generated by the trial were highly dependent upon the inclusion criteria and clinical circumstances surrounding the trial. Inclusion criteria for the US clinical trial included a transvaginal ultrasound of each pregnancy to precisely determine gestational age, as well as to rule out ectopic pregnancy. Each practitioner who dispensed mifepristone was a physician experienced in surgical abortion with admitting privilege at an emergency care facility capable of resuscitation and surgical evacuation located within 1 hour of the patient.[23]

In contrast, the final mifepristone procedure approved by the FDA does not require ultrasound confirmation of gestational age and intrauterine location, does not require that the dispensing practitioner be a physician or that the practitioner have any skills in surgical abortion, ultrasound dating of gestational age, or even any skills in handling the known complications of the mifepristone regimen. The FDA also did not retain requirements governing physician training in the use of mifepristone or the 4-hour waiting period after misoprostol is given. The FDA should not have extrapolated conclusions about the safety and efficacy of its approved regimen from data generated under trial conditions not mirroring the approved regimen. Effectively, therefore, the agency approved a drug regimen that it had not tested.

Mifepristone Regimen Unsafe for American Women

LACK OF MANDATORY ULTRASOUND CONFIRMATION OF GESTATIONAL AGE INCREASES THE RISK OF ADVERSE EVENTS DURING MIFEPRISTONE ABORTIONS

The failure rate of mifepristone/misoprostol from the US clinical trial was 8% at ≤49 days' gestation, 17% at 50–56 days' gestation, and 23% at 57–63 days' gestation.[6]

> Failures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of pregnancy. The largest increase was in failures representing ongoing pregnancy, which increased from 1% in the ≤49 days' group to 9% in the 57–63 days' group ($p < 0.001$). Abdominal pain, nausea, diarrhea, and vaginal bleeding also increased with advancing gestational age. Two percent of the women in the ≤49 days' group as compared with 4% in each of the other two groups were hospitalized, underwent surgical intervention, and received intravenous fluids ($p < 0.008$).

Thus, a precise knowledge of the gestational age of the pregnancy is critically important for minimizing adverse events such as excessive bleeding necessitating emergency surgical intervention and transfusion and retained tissue leading to increased risk of infection. Such precision in dating (±1 wk) can be obtained only by ultrasound and, indeed, an ultrasound for gestational age confirmation was required for inclusion in the US trial. However, the FDA did not require ultrasound before administration of mifepristone. The only way to ensure intrauterine location is by ultrasound, which te FDA did not require prior to mifepristone administration.

Furthermore, the ultrasound requirement for inclusion in the US trial of mifepristone not only served to confirm gestational age, but also to rule out ectopic pregnancy. Ectopic pregnancies were excluded from the US clinical trial because mifepristone does not result in termination of an ectopic pregnancy. According to the practice guidelines published by the American College of Obstetrics and Gynecology[24]:

> Women may even experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac or even an ectopic pregnancy. She will undoubtedly interpret bleeding and pain as consistent with a pharmaceutical abortion, since these are nearly universal effects of mifepristone and misoprostol.

Since the symptoms of ectopic pregnancy mimic the symptoms of abortion by mifepristone, it is critically important that the pregnancy be documented to be intrauterine prior to administration of mifepristone. The only way to ensure intrauterine location is by ultrasound, which the FDA did not require prior to mifepristone administration.

LACK OF PROVIDER TRAINING INCREASES THE RISK OF SEVERE ADVERSE EVENTS DURING MIFEPRISTONE ABORTIONS

Since 2–4% of the subjects in the US trial required surgical termination, often under emergent circumstances, the skill and training of the abortion practitioner become of paramount importance in minimizing morbidity and mortality from the mifepristone/misoprostol abortion procedure. For this reason, the principal investigators at each site were limited to physicians who were experienced with surgical abortion techniques and had admitting privileges at a medical facility capable of emergency care located within one hour of the patient.[24] The FDA did not require similar skills in current mifepristone providers.

THE FDA'S FAILURE TO APPLY ADEQUATE RESTRICTIONS ON USE OF MIFEPRISTONE INCREASES THE DANGER OF SEVERE ADVERSE EVENTS

Prior to the final approval of mifepristone, the FDA proposed that providers of the mifepristone/misoprostol regimen must be licensed physicians who are trained to perform abortions and also trained to assess the gestational age of the pregnancy by ultrasound and diagnose an ectopic pregnancy by ultrasound. Furthermore, because of the frequent need for emergent surgical evacuation, the provider must have admitting privileges to a medical facility capable of resuscitation and surgical evacuation.[25] These restrictions would have made the postmarketing use of mifepristone/misoprostol mirror the clinical trial and, hopefully, minimized the significant risks of hemorrhage and retained tissue. However, these restrictions were opposed by abortion advocates as unreasonable.

The Population Council and Danco argued that nonphysicians should be able to dispense the drug and that the abortion provider need not have admitting privileges or even the skill to evacuate a uterus, since adequate follow-up care would be provided if the woman were simply directed to go to a local emergency department for heavy bleeding.[26] Ralph Hale MD, executive vice president of American College of Obstetricians and Gynecologists, and E Ratcliffe Anderson MD, executive vice president of the American Medical Association, wrote a letter to Dr Jane Henney of the FDA condemning the proposed restrictions, especially the requirement for ultrasound: "Requiring ultrasound to date a pregnancy or determine if there is an ectopic pregnancy is not required to administer the drug safely and correctly. Physicians and patients can quite accurately date a woman's pregnancy."[27]

Hale's statement stands in sharp contrast to data from the US clinical trial.[28] In a study comparing gestational age estimates based on the last reported menstrual period with those generated through ultrasound in patients presenting for medical abortion, the former method was shown to be significantly inaccurate in approximately half of the cases. The authors observed:

> It is interesting that in this population of women seeking abortion the gestational age according to the LMP [last menstrual period] was verified by the transvaginal ultrasonographic examination only 48% to 56% of the time when a gestational sac was present and only 55% to 64% of the time when an embryonic pole was present.… These results, though, do not even include those women who were excluded from the studies because the ultrasonographic examination findings were so different from the dates by LMP that the estimation of gestational age was changed too much for them to be included.

At the end of the political maneuvering, politics triumphed over patient safety, and the proposed FDA restrictions were gutted to impotency prior to approval of mifepristone.

MIFEPRISTONE HAS BEEN RESPONSIBLE FOR DEATHS AS WELL AS NUMEROUS SEVERE ADVERSE EVENTS IN NORTH AMERICA

On April 17, 2002, Danco, with FDA assistance, issued a letter to healthcare providers to alert them to "New Safety Information" that included a number of reports of serious adverse events that had been experienced by women who were undergoing or had recently completed the mifepristone regimen.[29] The FDA obtained this information through its voluntary Adverse Event Reporting system. A number of patients had developed ruptured ectopic pregnancies; one of these women died from hemorrhage. The letter also reported "two cases of serious systemic bacterial infection (one fatal)." The fatality apparently precipitated a halt in the Population Council's Canadian clinical trials of mifepristone.[30] Most recently, an 18-year-old woman in California died, apparently of overwhelming sepsis during her mifepristone abortion. Finally, a 21-year-old woman suffered a myocardial infarction 3 days after she completed the mifepristone regimen.[31-37] Two of the patients who were reported to have developed life-threatening adverse events were 15 years old.[38,39]

The FDA acknowledged that these life-threatening events are rare in healthy women and yet had occurred during the mifepristone abortion process.[40] With respect to bacterial infection, for example, the FDA observed that[38,39]:

> the rate of serious infection as a complication of pregnancy is 3.5 per 1000 pregnancies. Uterine infection occurs in 0.1–4.7% of first trimester surgical abortions and in 0.0–6.1% of medical abortions. In the past, it was most often associated with illegal abortions. It rarely occurs with pelvic surgery or even with otherwise normal childbirth.

The FDA similarly noted the unusual nature of a myocardial infarction in a young woman[38,39]:

> The single heart attack occurred in a 21 year old. A heart attack in very young women is extremely rare.… In 1997, the rate among US women aged 20–24 years was 0.19 per 100 000 women.

The occurrence of 2 cases of fatal bacterial infection, as well as a myocardial infarction in a 21-year-old woman, is cause for significant concern. The real ratio of serious adverse events to total uses of the mifepristone regimen is only speculative because serious adverse event reporting is voluntary and, thus, likely incomplete and because it is not publicly known how many times the mifepristone regimen has been used.

The precedent for responding to events of such severity within the healthcare industry has been set. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has developed an approach for investigating adverse events similar in gravity to those that prompted the issuance of the letter to healthcare providers. The JCAHO looks for "sentinel events" that are "unexpected occurrences" involving death or serious physical or psychological injury, or the risk thereof.[41] Sentinel events signal the need for the commencement of a root cause analysis of the events. It is particularly important that the FDA react to these sentinel events because the clinical trials underlying the approval of the mifepristone regimen did not adhere to the FDA's endorsed scientific methodology for such trials. The substandard trial design of the US and French clinical trials precluded an accurate estimation of the safety of mifepristone compared with the existing available alternatives. Moreover, the FDA did not require the sponsor to conduct rigorous Phase IV studies, which could have compensated for some of these deficiencies by generating additional safety data

Summary

The approval and use of mifepristone as an abortifacient in the US have been shrouded in controversy. Deviations from evidence-based medicine standards of research cast doubt on the safety of the current use of this drug. At least 2 preventable fatalities have occurred in the US, not to mention other life-threatening complications. Numerous violations of the FDA's own procedural rules demand a revocation of the approval of mifepristone as an abortifacient. The Citizen Petition requesting this revocation, filed in August 2002, has documented these and numerous other safety concerns. To date, the RU-486 Suspension and Review Act currently before Congress suspends the approval of mifepristone as an abortifacient and calls for Congressional review of the conduct of the FDA in that approval.[42,43]

Byron C Calhoun MD FACOG FACS, Division of Maternal-Fetal Medicine; Director, Antepartum Diagnostic Center, Rockford, IL

Donna J Harrison MD, Chairman, Subcommittee on Mifeprex, American Association of Pro Life Obstetricians and Gynecologists, Holland, MD

Reprints: Donna J Harrison MD, American Association of Pro Life Obstetricians and Gynecologists, 844 S. Washington, Suite 1600, Holland, MI 49423.

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Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: December 12, 2003

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word '*Select*' and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY 1
AUDITORY/EAR 2
BLOOD/BONE MARROW 4
CARDIAC ARRHYTHMIA 5
CARDIAC GENERAL 7
COAGULATION 10
CONSTITUTIONAL SYMPTOMS 11
DEATH 13
DERMATOLOGY/SKIN 14
ENDOCRINE 17
GASTROINTESTINAL 19
GROWTH AND DEVELOPMENT 29
HEMORRHAGE/BLEEDING 30
HEPATOBILIARY/PANCREAS 34
INFECTION 35
LYMPHATICS 38
METABOLIC/LABORATORY 40
MUSCULOSKELETAL/SOFT TISSUE 43
NEUROLOGY 47
OCULAR/VISUAL 52
PAIN 55
PULMONARY/UPPER RESPIRATORY 56
RENAL/GENITOURINARY 60
SECONDARY MALIGNANCY 63
SEXUAL/REPRODUCTIVE FUNCTION 64
SURGERY/INTRA-OPERATIVE INJURY 66
SYNDROMES 68
VASCULAR 70

ALLERGY/IMMUNOLOGY

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash, flushing; urticaria, dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

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[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – *Select:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – *Select*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

Page 1 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis, symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer.						
ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select*.						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select*.						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).						
ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic.						
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

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[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS

Page 2 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select*' is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

Page 2 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration, ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care, medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone).						
ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

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[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic, dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea.						
ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—

REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow.

ALSO CONSIDER: Salivary gland changes/saliva.

Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death

REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*.

ALSO CONSIDER: Dehydration; Esophagitis.

Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death

ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).

Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death

REMARK: Esophagitis includes reflux esophagitis.

ALSO CONSIDER: Dysphagia (difficulty swallowing).

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits), IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis, significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death

ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic, altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

Page 1 of 4

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time), Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

Page 4 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*, Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin. ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

Page 1 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC $<1.0 \times 10^9$/L, fever ≥ 38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L) – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection (documented clinically) – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

Page 2 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

Page 1 of 2

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis.						
ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

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[4] Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY

Page 3 of 3

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure, Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

Page 1 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select.*						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE

Page 2 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

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[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK).						
ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

Page 4 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

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[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

Page 2 of 5

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache, postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

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[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Neuropathy cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste –CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening, disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*.						
ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision or restraints indicated	Harmful to others or self; life-threatening consequences	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling, paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness, Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

Page 1 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain, pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

Page 1 of 4

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes)						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest, intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select:* – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g . thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select*; Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal, enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

Page 2 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

<table>
<tr><th colspan="7">SURGERY/INTRA-OPERATIVE INJURY Page 1 of 2</th></tr>
<tr><th></th><th></th><th colspan="5">Grade</th></tr>
<tr><th>Adverse Event</th><th>Short Name</th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td colspan="7">NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.</td></tr>
<tr><td>Intra-operative injury – <i>Select Organ or Structure</i>
'<i>Select</i>' AEs appear at the end of the CATEGORY.</td><td>Intraop injury – <i>Select</i></td><td>Primary repair of injured organ/structure indicated</td><td>Partial resection of injured organ/structure indicated</td><td>Complete resection or reconstruction of injured organ/structure indicated</td><td>Life threatening consequences; disabling</td><td>—</td></tr>
<tr><td colspan="7">REMARK: The '<i>Select</i>' AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.</td></tr>
<tr><td>Intra-operative Injury – Other (Specify, __)</td><td>Intraop Injury – Other (Specify)</td><td>Primary repair of injured organ/structure indicated</td><td>Partial resection of injured organ/structure indicated</td><td>Complete resection or reconstruction of injured organ/structure indicated</td><td>Life threatening consequences; disabling</td><td>—</td></tr>
<tr><td colspan="7">REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the '<i>Select</i>' AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.</td></tr>
</table>

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE *(continued)*
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL *(continued)*
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

  NERVES:
  - Brachial plexus
  - CN I (olfactory)
  - CN II (optic)
  - CN III (oculomotor)
  - CN IV (trochlear)

NEUROLOGY *(continued)*

  NERVES:
  - CN V (trigeminal) motor
  - CN V (trigeminal) sensory
  - CN VI (abducens)
  - CN VII (facial) motor-face
  - CN VII (facial) sensory-taste
  - CN VIII (vestibulocochlear)
  - CN IX (glossopharyngeal) motor pharynx
  - CN IX (glossopharyngeal) sensory ear-pharynx-tongue
  - CN X (vagus)
  - CN XI (spinal accessory)
  - CN XII (hypoglossal)
  - Cranial nerve or branch NOS
  - Lingual
  - Lung thoracic
  - Peripheral motor NOS
  - Peripheral sensory NOS
  - Recurrent laryngeal
  - Sacral plexus
  - Sciatic
  - Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

Page 2 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

Page 1 of 2

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening, pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/embolism	Thrombosis/thrombus/embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death

NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.

VASCULAR

Page 2 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e g , claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening, disabling; evidence of end organ damage	Death
Navigation Note: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
Also Consider: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

BEFORE THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Citizen Petition re: Request for)
Stay and Repeal of the Approval of)
Mifeprex (mifepristone) for the Medical)
Termination of Intrauterine Pregnancy)
through 49 Days' Gestation)

CITIZEN PETITION AND REQUEST FOR ADMINISTRATIVE STAY

The American Association of Pro Life Obstetricians and Gynecologists ("AAPLOG"), the Christian Medical Association ("CMA"), and Concerned Women for America ("CWA") (collectively, "the Petitioners") submit this Petition pursuant to 21 C.F.R. §§ 10.30 and 10.35; 21 C.F.R. Part 314, Subpart H (§§ 314.500-314.560); and Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355).[1] The Petitioners urge the Commissioner of Food and Drugs to impose an immediate stay of the approval by the Food and Drug Administration ("FDA" or "agency") of Mifeprex™ (mifepristone; also, "RU-486"),[2] thereby halting all distribution and marketing of the drug, pending final action on this Petition. In addition the Petitioners urge the Commissioner to revoke FDA's approval of Mifeprex and request a full FDA audit of the Mifeprex clinical studies.[3]

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[1] Federal Food, Drug, & Cosmetic Act of 1938 ("FD&C Act"), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*).

[2] The New Drug Application for Mifeprex, which was filed by the Population Council, was approved on September 28, 2000. Mifeprex is distributed by Danco Laboratories, a licensee of the Population Council.

[3] The Petitioners will, at times, cite to documents contained in FDA's January 31, 2002 public release of documents (approximately 9,000 pages in 94 files) made pursuant to a Freedom of Information Act request ("FDA FOIA Release") filed by the non-profit organization, Judicial Watch. These bracketed citations will reflect the page numbering FDA has stamped on the bottom of each page, for example: [FDA FOIA Release: MIF 000001-05]. The FDA webpage posting the 94 files is: <http://www.fda.gov/cder/archives/mifepristone/default.htm>. Since the initial release FDA has edited some of the 94 files. However, the stamped page numbers have not changed. Additionally, many footnotes refer to Appendix A to this Petition, which contains a selected bibliography.

I. ACTION REQUESTED

The Petitioners respectfully request that the Commissioner immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on this Petition. They urge the Commissioner to revoke market approval for Mifeprex in light of the legal violations and important safety concerns explained below. In addition, they request a full FDA audit of all records from the French and American clinical trials offered in support of the Mifeprex NDA.

II. INTEREST OF THE PETITIONERS

While it is true that the Petitioners have consistently opposed abortion and continue to do so, a careful examination of the claims made in this petition should alert people of conscience on either side of this issue that women are being harmed. Regardless of one's position on abortion, FDA's violations of its standards and rules have put women's health and lives at risk. The Petitioners are non-profit organizations that share a great concern about women's health issues. The American Association of Pro-Life Obstetricians and Gynecologists ("AAPLOG") is a recognized interest group of the American College of Obstetricians and Gynecologists ("ACOG"), currently representing over 2,000 obstetricians and gynecologists throughout the United States of America. The Christian Medical Association, founded in 1931, is a professional organization with thousands of physician members representing every medical specialty. Concerned Women for America ("CWA"), founded in 1979, is the largest public policy women's organization in the United States with members in every State and a total membership exceeding 500,000.

III. STATEMENT OF GROUNDS

A. SUMMARY OF THE PETITIONERS' ARGUMENTS

Good cause exists to grant an immediate stay of the agency's September 28, 2000 Mifeprex approval.[4] Good cause also exists for the subsequent revocation of that approval.[5] As established herein, (1) the approval of Mifeprex violated the Administrative Procedure Act's prohibition on agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;[6] (2) FDA's approval of Mifeprex violated 21 U.S.C. § 355 because the drug does not satisfy the safety and labeling requirements of that section; and (3) the agency approved Mifeprex despite the presence of substantial risks to women's health.

This Petition represents the latest attempt by members of the medical community and other concerned observers to warn FDA of the dangers posed by Mifeprex abortions to the health of women.[7] Women undergoing Mifeprex abortions risk, among other problems, uncontrolled fatal hemorrhage and serious bacterial infections. Mifeprex abortions particularly endanger women with ectopic pregnancies and those whose pregnancies have progressed beyond 49 days.[8]

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[4] When FDA approved the Population Council's NDA for mifepristone, it approved the drug for use in conjunction with misoprostol. In this Petition, "Mifeprex Regimen" will refer to the combined use of Mifeprex and misoprostol to effect an abortion.

[5] *See* 21 C.F.R. § 314.530 ("Withdrawal Procedures").

[6] 5 U.S.C. § 706(2)(A).

[7] On February 28, 1995, Americans United for Life and other groups and individuals filed a Citizen Petition with FDA requesting it to "refuse to approve any NDA for RU 486 for use as a pharmaceutical abortifacient that does not contain adequate evidence that the drug has undergone nonclinical and clinical safety and effectiveness trials." The petitioners also set forth a number of factors for the agency to consider. Americans United for Life *et al.*, Citizen Petition (Feb. 28 1995)[FDA FOIA Release: MIF 006144-6248]; *see also*, Letter, Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, FDA, to Gary L. Yingling, McKenna & Cuneo (March 20, 1995) (one-page letter suggesting that the petition was prematurely filed and claiming to be a "full response")[FDA FOIA Release: MIF 006250].

[8] The gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy. On Day 49, a woman is deemed to be seven weeks pregnant, which means she has experienced 49 days of amenorrhea (time elapsed since the beginning of her last menstrual period).

Warnings about these dangers, together with FDA's own concerns about the safety of the abortion regimen, went unheeded. On September 28, 2000, FDA approved the new drug application ("NDA") for Mifeprex.[9] The initial reports of life-threatening and fatal adverse events appear to bear out the safety concerns underlying the pre-approval warnings. The Petition highlights a number of agency actions that were arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law. These serious departures from standard agency practice allowed the NDA for Mifeprex, a drug that is not safe for its intended use, to be approved by FDA.[10]

First, the approval of Mifeprex violated the legal requirements of FDA's Accelerated Approval Regulations found in Subpart H.[11] Mifeprex is not a drug for the treatment of a serious or life-threatening illness. It does not demonstrate the potential to address an unmet medical need because a less dangerous and more effective alternative for performing abortions already exists. It appears that FDA's decision to use Subpart H was motivated by its concern that, without restrictions, the drug could not be used safely. Rather than attempting to compensate for

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Ovulation for the small percentage of woman with a perfect 28 day cycle typically takes place between Days 12 and 14 and fertilization typically takes place 24 to 48 hours later.

[9] *See* U.S. Department of Health and Human Services, *HHS News*, Press Release P00-19, "FDA Approves Mifepristone for the Termination of Early Pregnancy," September 28, 2000. A selection of FDA documents relevant to its approval of Mifeprex may found at: <http://www.fda.gov/cder/drug/infopage/mifepristone>; and on a second page: <http://www.fda.gov/cder/foi/nda/2000/20687_mifepristone.htm>.

[10] FDA's unlawful approval of Mifeprex may not be unprecedented. The medical-scientific community and the mainstream press have called attention to a number of other instances in which one could question whether drugs and medical devices have been improperly approved. *See, e.g.*, Richard Horton, "Lotronex and the FDA: A Fatal Erosion of Integrity," *Lancet* 357 (May 19, 2001): 1544-1545; David Willman, "How a New Policy Led to Seven Deadly Drugs," *Los Angeles Times* (Dec. 20, 2000): at A1; Kit R. Roane, "Replacement Parts: How the FDA Allows Faulty, and Sometimes Dangerous, Medical Devices onto the Market," *U.S. News & World Report* (July 29, 2002): 54-59 (discussing FDA's recent approval policies regarding medical devices).

[11] 21 C.F.R. §§ 314.500-314.560. FDA's Accelerated Approval Regulations are set forth at 21 C.F.R. Part 314, Subpart H ("Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses") ("Accelerated Approval Regulations" or "Subpart H"). The Accelerated Approval Regulations were promulgated by FDA after notice and comment: New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Proposed Rule*, 57 Fed. Reg. 13234 (April 15, 1992) ("*Subpart H Proposed Rule*") and New Drug, Antibiotic, and Biological

the inherent dangerousness of Mifeprex by inappropriately resorting to the Subpart H approval mechanism, FDA should simply have refused to approve Mifeprex. (*See* Section III.D., *infra.*)

Second, Mifeprex was not proven to be "safe and effective" as required by law.[12] The scientific quality of the trials used to support the NDA was undeniably deficient according to Congress's statutory requirements and FDA's well-established standards.[13] The trials were not blinded, randomized, or concurrently controlled. FDA failed to explicitly waive its rules or offer a reasoned explanation for defying its own standards. (*See* Section III.E., *infra.*)

Third, the Mifeprex Regimen requires that Mifeprex be used in conjunction with another drug, misoprostol. FDA, however, has never approved misoprostol as an abortifacient. Although FDA normally opposes the promotion of off-label uses, in connection with the Mifeprex NDA, the agency sanctioned and itself participated in the promotion of the off-label use of misoprostol. Mifeprex, the label of which creates the false impression that misoprostol is approved for use as an abortifacient, is misbranded. (*See* Section III.F., *infra.*)

Fourth, and most critically, the Mifeprex Regimen is dangerous. FDA sought, without success, to convince the drug sponsor to place safety restrictions on Mifeprex. When that failed, on June 1, 2000, FDA itself proposed restrictions intended to reduce the unacceptable health risks associated with mifepristone abortions. Nevertheless, the agency, under concerted pressure from abortion advocates and politicians, ultimately approved mifepristone for use in a deregulated regimen that lacks key safeguards. For example, the regimen does not include a requirement that transvaginal ultrasound be used to date pregnancies and rule out ectopic

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Product Regulations; Accelerated Approval, *Final Rule*, 57 Fed. Reg. 58942 (Dec. 11, 1992) ("*Subpart H Final Rule*") (available at: <http://www.fda.gov/cder/fedreg/fr19921211.txt>).

[12] *See* 21 U.S.C. § 355.

[13] *See* 21 C.F.R. § 314.126.

pregnancies, which cannot be treated with the Mifeprex Regimen. In addition, FDA failed to restrict access to mifepristone to physicians trained in the provision of Mifeprex and surgical abortions and capable of treating complications arising from abortions. Concerns about the dangers of Mifeprex were confirmed when Danco and FDA announced publicly on April 17, 2002, a number of serious adverse events, including two deaths. (*See* Section III.G., *infra.*)

Fifth, the drug's sponsor has neglected to require Mifeprex providers to adhere to the limited restrictions contained in the approved regimen. The sponsor's inaction is surprising in light of the fact that these restrictions are being flouted openly. Section 314.530 authorizes FDA to withdraw the approval of a Subpart H drug if a drug's sponsor does not fulfill its responsibility of ensuring compliance with the restrictions on the use of the drug. (*See* Section III.H., *infra.*)

Sixth, the safeguards employed in the U.S. Clinical Trial are not mirrored in the regimen that FDA approved. Transvaginal ultrasounds, for example, although employed in the U.S. Clinical Trial, are not required under FDA's approved regimen. Nor are the trial requirements governing emergency care reproduced in the approved regimen. (*See* Section III.I., *infra.*)

Seventh, FDA's waiver of its rule, 21 C.F.R. § 314.55, requiring the testing of all new drugs for their potential effects on children, has jeopardized the health and safety of American teenage girls who may have abortions. FDA expressly contemplated the pediatric use of Mifeprex, but waived, without an adequately reasoned justification, the requirement that the drug undergo pediatric testing. (*See* Section III.J., *infra.*)

Eighth, FDA did not require the sponsor of Mifeprex to honor its commitments for Phase IV studies, which provide the opportunity to study in-depth the drug's safety and effectiveness after approval. When FDA approved Mifeprex, the agency permitted the Population Council to replace the six Phase IV study commitments it had made in 1996 with two much narrower commitments. The modified studies will not adequately address outstanding questions, such as the effects of mifepristone abortions on women outside the tested age range of 18 to 35 years. (*See* Section III.K., *infra.*)

In sum, FDA, in approving Mifeprex, acted in a manner inconsistent with its statutory authorization, regulations, and well-established policies. FDA did not provide a contemporaneous explanation of its numerous departures from past practice.[14] Its aberrant actions coupled with the absence of explanations violated a fundamental principle of administrative law; an agency must either adhere to prior policies or fully explain why it is not doing so.[15] The approval of Mifeprex was, therefore, arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. It must be reversed.

B. FDA APPROVAL OF THE MIFEPREX REGIMEN

1. The Introduction of Mifepristone into the United States

Roussel Uclaf, a French pharmaceutical firm, first developed and tested mifepristone ("RU-486") as an abortifacient. By April 1990 the drug had become permanently available in

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[14] An agency must explain its reasons for acting in a particular manner. *See, e.g., Securities & Exchange Commission v. Chenery Corp.*, 332 U.S. 194, 196-97 (1947) (noting that a court should not "be compelled to guess at the theory underlying the agency's action," but rather "[i]f the administrative action is to be tested by the basis upon which it purports to rest, that basis must be set forth with such clarity as to be understandable."). *Post hoc* rationalizations cannot salvage the agency's action with respect to Mifeprex. *See, e.g., Martin v. Occupational Safety and Health Review Commission*, 499 U.S. 144, 156-57 (1991) (*post hoc* rationalizations of counsel "do not constitute an exercise of the agency's delegated lawmaking powers"); *Investment Company Institute v. Camp*, 401 U.S. 617, 628 (1971) ("Congress has delegated to the administrative official and not to appellate counsel the responsibility for elaborating and enforcing statutory commands.").

[15] *See, e.g., Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir. 1970) ("[A]n agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored, and if an agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute.") (footnote omitted) (citing approvingly *Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Ins. Co* , 463 U.S. 29, 57 (1983)); *JSG Trading Corp. v. USDA*, 176 F.3d 535, 544 and 545 (D.C. Cir. 1999) (remanding agency action where "the agency manifestly failed to explain its abrupt departure from prior precedent" and noting that the agency "was obligated to articulate a principled rationale for departing from [its prior] test") (citations omitted); *Gilbert v. National Labor Relations Board*, 56 F.3d 1438, 1445 (D.C. Cir. 1995) ("It is, of course, elementary that an agency must conform to its prior decisions or explain the reason for its departure from such precedent.").

France. According to Dr. André Ulmann, the Roussel project manager for the development of RU-486, Roussel prohibited the commencement of any new studies in the United States and took the position that "under no circumstance[s]" would it permit a new drug application to be filed with FDA.[16] In fact, "the chairman of Hoechst [the parent company to Roussel] had officially declared that mifepristone was not compatible with the ethics of the company."[17]

Undeterred by Hoechst's reluctance to bring the drug to the United States, on January 22, 1993, President Clinton directed Department of Health and Human Services ("HHS") Secretary Donna Shalala to assess initiatives to promote the testing and licensing of mifepristone or other antiprogestins in the United States.[18] Further signaling that approval of mifepristone by FDA was a top priority of his Administration, President Clinton reportedly "wrote to Hoechst asking the company to file a new drug application with the FDA (an unprecedented situation in the pharmaceutical industry!), which Hoechst intransigently refused to do."[19]

In early 1993, Secretary Shalala and FDA Commissioner David Kessler "communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the American marketplace."[20] On May 16, 1994, the Population Council reached an agreement with Roussel Uclaf, pursuant to which the European drug maker transferred "without remuneration, its United States patent rights for mifepristone (RU-486) to the Population Council . . . ."[21] Secretary Shalala was instrumental in bringing about the transfer of the patent rights to the Population Council[22] and even set a deadline – May 15, 1994 – for the transfer.[23]

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[16] *See* André Ulmann, M.D., "The Development of Mifepristone: A Pharmaceutical Drama in Three Acts," *Journal of the American Medical Women's Association* 55 (Supplement 2000): 117-20, at 119. In 1994 Roussel Uclaf joined with the German pharmaceutical firm, Hoechst AG, to form Hoechst Roussel Ltd. In 1995, this entity merged with a third firm, Marion Merrell Dow, to form Hoechst Marion Roussel. In December 1999 Hoechst and Rhône-Poulenc combined to form Aventis, S.A., headquartered in Strasbourg, France.

[17] Ulmann, *infra* Appendix A, at 120.

[18] *See* Memorandum for the Secretary of Health and Human Services, "Importation of RU-486," *Public Papers of the Presidents: Administration of William J. Clinton, 1993* (Jan. 22, 1993) at 11.

[19] Ulmann, *infra* Appendix A, at 120 (emphasis in original).

[20] HHS Fact Sheet, "Mifepristone (RU-486): Brief Overview," (rel. May 16, 1994). Available at: <http //www.hhs.gov/news/press/pre1995pres/940516.txt>.

After obtaining the American patent rights to mifepristone, the Population Council conducted clinical trials in the United States and filed a new drug application in 1996. The Population Council established a non-profit corporation, American Health Technologies ("AHT"), to assist in the effort to bring the drug to the market.[24] The Population Council ultimately granted Danco Laboratories, LLC ("Danco"), which was incorporated in the Cayman Islands in 1995, "an exclusive license to manufacture, market, and distribute Mifeprex in the United States."[25] Danco, after a difficult search,[26] selected the Chinese drug manufacturer,

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[21] HHS Press Release, "Roussel Uclaf Donates U.S. Patent Rights for RU-486 to Population Council," (rel. May 16, 1994). Available at: <http://www.hhs.gov/news/press/pre1995pres/940516.txt>.

[22] *Id.* ("Shalala commended Roussel Uclaf and the Population Council for coming to closure after months of complex negotiations amid repeated urging from the Clinton administration.")

[23] *See* William J. Eaton, "Path Cleared for Abortion Pill Use Medicine: French Maker of RU-486 Gives Patent Rights to a Nonprofit Group," *Los Angeles Times*, May 17, 1994, at A1 ("Negotiations between the French manufacturer and the Population Council dragged on for more than a year until Shalala set a May 15 deadline, producing the agreement . . . .").

[24] Dr. Susan Allen, who once served as president and CEO of American Health Technologies, joined the staff of the Reproductive and Urologic Drug Products Division in FDA's Center for Drug Evaluation and Research in 1998 as a medical officer and was promoted to team leader for reproductive drugs in January 1999. *See* "RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director," *The Pink Sheet* 62 (June 12, 2000): at 14. Dr. Allen became acting director of the Division in January 2000 and permanent director on June 18, 2000. *See id. The Pink Sheet* also commented, "Allen is presumably recused from the mifepristone review as a result of her prior experience with the product." *Id.*

[25] Danco, "The History of Mifeprex,"available at <http://www.earlyoptionpill.com/history.php3>. (Danco has dubbed mifepristone "the Early Option Pill" for marketing purposes.) Little information about Danco is available. *See* Robert O'Harrow, "RU-486 Marketer Remains Elusive," *Washington Post* (Oct. 12, 2000): at A18 ("Secretive and obscure, Danco is one of the most enigmatic companies in the pharmaceutical industry."). Danco is apparently a successor entity to Advanced Health Technology. *See* "RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director," *The Pink Sheet* 62 (June 12, 2000): at 14 (reporting that Advanced Health Technologies had become Neogen, which, in turn, had become Danco, according to the Population Council and Danco, "with some management and investor changes").

[26] In 1995 Danco contracted with a Hungarian pharmaceutical firm, Gideon Richter, to manufacture mifepristone for American distribution. After Gideon Richter reneged on the contract in February 1997, Danco sued Gideon Richter for breach of contract and began searching for a new producer. *See* "Ru-486: U.S. Partners Sue European Manufacturer," *Kaiser Daily Reproductive Health Report* (June 12, 1997) (available at: <http://www.kaisernetwork.org/reports/1997/06/a970612.1.html>). This was one of a number of lawsuits stemming

Shanghai Hua Lin Pharmaceutical Company, to manufacture the drug.[27] Abortion advocates eagerly awaited the approval of mifepristone in the United States because, among other reasons, they anticipated that it would enhance women's access to abortion.[28]

2. FDA Approval of Mifepristone

The Population Council filed a new drug application for "mifepristone 200 mg tablets" on March 18, 1996.[29] FDA initially accorded the drug standard review, but in a letter dated May 7, 1996, FDA's Center for Drug Evaluation and Research notified the Population Council that mifepristone would receive priority review.[30] On September 18, 1996, FDA issued a letter

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from attempts to bring mifepristone to the United States. *See* "Ru-486: Litigation Could Cause Delay For U.S. Introduction," *Kaiser Daily Reproductive Health Report* (Dec. 17, 1996) (available at: <http://www.kaisernetwork.org/reports/1996/12/a961217.9.html>) (describing some of the legal problems encountered by the Population Council in bringing the drug to market).

[27] Pamela Wiley, "Chinese Plant to Make RU-486 for U.S.," (Oct. 15, 2000) (available at: <http://www.nurseweek.com/news/00-10/1015-486.asp>).

[28] *See* Margaret Talbot, "The Little White Bombshell," *New York Times Magazine* (July 11, 1999): at 39-43 ("'One of my real, and I think realistic, hopes for this method,' says Carolyn Westhoff, an OB-GYN at Columbia University medical school who offers medical abortion as part of a clinical trial, 'is that it will help get abortion back into the medical mainstream and out of this ghettoized place it's been in.' And if that is indeed the scenario we're looking at – a scenario in which abortion is folded far more seamlessly into regular medical practice – then it has implications not only for women's experience of abortion but for the politics of abortion as well."); *id.* ("Not only are mifepristone abortions, by nature, more discreet than their surgical equivalents (like vacuum aspiration), but the practitioners who prescribe them will almost certainly constitute a larger and a more varied group than the dwindling corps of OB-GYNs willing to do surgical abortions.") In fact, access to medical abortion, will continue to depend on the availability of surgical abortion, which serves as a back-up in FDA's approved Mifeprex regimen. Thus, it is spurious to suggest that Mifprex abortions can safely be made available in places in which surgical abortion is not offered.

[29] The application was dated March 14, 1996 and received by FDA on March 18, 1996. *See* Letter, FDA/CDER to Ann Robbins, Population Council (Sept. 18, 1996): at 1 ("1996 Mifepristone Approvable Letter").

[30] *See* Letter, FDA/CDER to Ann Robins, Population Council (May 7, 1996)[FDA FOIA Release: MIF 006431]. The Population Council filed its complete response on March 30, 2000, which gave FDA until September 30, 2000 to act on the application. In fiscal year 2000 a "standard" designation would have given FDA at least ten months to consider the application. FDA accorded mifepristone "priority review," which typically required FDA to act within six months. *See* FDA/CDER, "PDUFA Reauthorization Performance Goals and Procedures" (Nov. 16, 1997) (available at: <http://www.fda.gov/cder/news/pdufagoals.htm>) ("Fiscal Year 2000"). Of 98 approvals in 2000, only 20 were Priority Review drugs. *See* FDA/CDER, *Report to the Nation* (2000): at 6. FDA's use of priority review appears inappropriate when considered in light of the agency's current guidance on the issue, which states that priority review is appropriate when "[t]he drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease." *See* FDA/CDER, "Review Management: Priority Review Policy," Manual of Policies and Procedures (MAPP) 6020.3, at 1 (Apr. 22, 1996) (text bracketed as in original).

stating that the application was approvable and requested more information from the sponsor.[31] FDA issued a second approvable letter for mifepristone, dated February 18, 2000, setting forth the remaining prerequisites for approval.[32] The 2000 Mifepristone Approvable Letter announced that FDA had "considered this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and [had] concluded that restrictions as per [21] CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[33]

On September 28, 2000, FDA approved mifepristone ("Mifeprex™") "for the medical termination of intrauterine pregnancies through 49 days' pregnancy."[34] Mifeprex was approved under Subpart H, which, FDA explained, "applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with certain skills or experience."[35] The approved regimen requires at least three office visits.[36] FDA required the Population Council to include, on the Mifeprex Label, a "black box warning for special problems, particularly those that may lead to death or serious injury."[37]

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[31] 1996 Mifepristone Approvable Letter at 1.

[32] 2000 Mifepristone Approvable Letter at 1.

[33] 2000 Mifepristone Approvable Letter at 5.

[34] Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000): at 1 ("Mifeprex Approval Letter"). In conjunction with the Mifeprex Approval Letter, FDA issued a memorandum that expanded upon the basis for and the restrictions on the approval of Mifeprex. *See* Memorandum, FDA/CDER to "NDA 20-687 MIFEPREX (mifepristone) Population Council" (Sept. 28, 2000): at 6 ("Mifeprex Approval Memo").

[35] Mifeprex Approval Memo at 6.

[36] Pursuant to the approved regimen, on "Day One: Mifeprex Administration" the patient reads the Medication Guide, signs the Patient Agreement, and ingests 600 mg of Mifeprex; on "Day Three: Misoprostol Administration" the patient ingests 400 micrograms of misoprostol orally (unless abortion has occurred and been confirmed by clinical examination or ultrasonographic scan); and, on or about "Day 14: Post-Treatment Examination" the patient returns to the practitioner for verification through a clinical examination or ultrasound that the pregnancy has been successfully terminated. *See* Mifeprex Label ("Dosage and Administration")(available at: <http://www.fda.gov/cder/foi/label/2000/20687lbl.pdf>).

[37] Mifeprex Approval Memo at 2 (citing 21 CFR 201.57(e), which authorizes FDA to require such a warning). The terms "label," "labeling," and "package insert" are often used interchangeably in food and drug law literature. In this Petition, "Label" describes the fine-print "package insert" that accompanies a drug when it is purchased. However, the FD&C Act defines "label" as "a display of written, printed, or graphic matter upon the immediate container of any article . . . ." 21 U.S.C. § 321(k). The term "labeling," which will also appears in this Petition,

FDA also outlined the Population Council's post-approval, Phase IV study commitments[38] and waived, without explanation, FDA's regulations providing that all new drugs must be tested for safety and effectiveness in children.[39]

C. BACKGROUND ON FDA'S DRUG APPROVAL PROCESS

1. FDA's Default Rules for Establishing Drug Safety and Effectiveness

FDA's regulations state that "[t]he purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."[40] FDA's default criteria for establishing safety and effectiveness are commonly referred to as the agency's "gold standard."[41] At the core of this default standard is FDA's recognition, reflecting the development of the scientific method and its application to pharmacology, that human bias and misperceptions are pervasive and that every precaution must be taken to avoid them. "The history of experimental medicine and research psychology," Michael Greenberg writes, "had demonstrated that uncontrolled, unblinded clinical trials were systematically vulnerable to experimenter bias, placebo effects, and the like."[42] Consequently, rigorous policies have been set forth by FDA and,

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encompasses "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). "Labeling" may even describe promotional materials used by the drug manufacturer including "[b]rochures, booklets, mailing pieces, . . . price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, . . . and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference) for use by medical practitioners, pharmacists, or nurses . . . ." 21 C.F.R. § 202.1(l)(2). FDA has provided more information on this terminology at: <http://www.fda.gov/cder/handbook/adverdef.htm>.

[38] *See* Mifeprex Approval Memo at 7.

[39] *See* FDA Mifeprex Approval Letter at 3.

[40] 21 C.F.R. § 314.126(a).

[41] *See* Jennifer Kulynych, "Will FDA Relinquish the 'Gold Standard' for New Drug Approval? Redefining 'Substantial Evidence' in the FDA Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 127-149, at 129. We will refer to these criteria as the "default standard."

[42] Michael D. Greenberg, "AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process," *Legislation and Public Policy* 3 (2000): 295-350, at 308.

more recently, by the International Conference on Harmonisation ("ICH") to eliminate bias from the evaluation of drug safety and effectiveness.[43]

FDA has been criticized for its zealous implementation of this policy,[44] but there is widespread recognition of the value of the default standard. The 1962 statutory amendments to the FD&C Act "authorized the agency to review all NDAs, not only to assess drug safety, but also to determine whether a manufacturer has provided 'substantial evidence' from 'adequate and well-controlled investigations' that a drug is effective for its intended use."[45] In implementing regulations, FDA "required that the evidence include at least one (and usually two) well-controlled (preferably 'blind') trials showing statistically significant results for treatment of humans with the new drug."[46] "[B]arring unusual circumstances, the agency ordinarily requires two successful and well-controlled clinical trials for new drug approval."[47] FDA's mandate for clinical trials "has two very important elements:"

> (1) a "controlled" trial, in which an experimental drug is compared to a placebo, or a known effective treatment in order to establish the comparative efficacy of the drug, and (2) a "double-blind" trial, which involves random assignment of research subjects to the

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[43] FDA, "International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials," *Notice*, 62 Fed. Reg. 66113 (Dec. 17, 1997) (*FDA Guidance (ICH: E8): General Considerations*). The homepage, (www.ich.org), for the ICH describes the organization as follows: "The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health."

[44] *See, e.g.*, Henry I. Miller, "Failed FDA Reform," *Regulation* 21 (Summer 1998): 24-30.

[45] Kulynych, *infra* Appendix A, at 129 (citing 21 U.S.C. § 355(d)).

[46] Greenberg, *infra* Appendix A, at 307 (citing 21 C.F.R. § 314.126 (1999). FDA comprehensively revised NDA evaluation rules in what is commonly referred to as the "NDA Rewrite." *See Final Rule*, "New Drug and Antibiotic Regulations," 50 Fed. Reg. 7452 (Feb. 22, 1985). Section 314.126 was promulgated in that final rule. *Id.* at 7506-7.

[47] Kulynych, *infra* Appendix A, at 130.

> experimental and control groups, under conditions in which neither the doctors nor the research subjects know who is getting the experimental drug and who the control.[48]

Each of the mandated features helps to eliminate bias in trial results. First, in "double-blinded" studies neither the patient nor the provider team (physician, nurse, etc.) knows the identity of the drug administered. If that is not possible, the person evaluating the trial results will not know which treatment has been administered to which subject. Second, a "randomized" study requires a random determination of which subject receives which treatment. This determination is often effected through computer-generated assignments done before clinical testing begins. Finally, comparison-control (also known as "comparator-control") requires that the experimental drug be compared *concurrently* to the current best treatment, or, alternatively, to a placebo. A placebo is used when the drug being tested represents the first treatment of its kind for the particular indication and no established treatment exists.

2. FDA Initiatives to Expedite the Approval of Drugs for the Very Sick

Largely in response to FDA's perceived slowness in approving drugs for human immunodeficiency virus ("HIV") patients, the agency undertook several initiatives to either expedite the ability of seriously or terminally-ill patients to have access to experimental drugs or to provide processes "intended to move drugs to market more quickly by compressing clinical development and FDA review times."[49] In 1988, FDA adopted an interim rule establishing Subpart E of 21 C.F.R. Part 312 ("Drugs Intended to Treat Life-Threatening and Severely-

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[48] Greenberg, *infra* Appendix A, at 307-8 (footnotes omitted).

[49] Sheila R. Shulman and Jeffrey S. Brown, "The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?" *Food and Drug Law Journal* 50 (1995): 503-531, at 503-4.

Debilitating Diseases").[50] Subpart E embodied several of the new procedures that FDA had used to bring the HIV medication, AZT (zidovudine), to market quickly.[51] Subpart E also created a "collaborative framework in which early and repeated consultation between the FDA and pharmaceutical manufacturers served to facilitate clinical trials, and to insure ex ante that prospective research designs would meet with subsequent regulatory approval."[52] "Taken together," the innovations found in Subpart E, "served to radically alter the new drug approval process with regard to life-threatening illnesses, particularly for AIDS."[53]

On April 15, 1992, FDA took its procedural innovations further when it proposed an "Accelerated Approval" process (*i.e.*, Subpart H). Shulman and Brown believe that Subpart H "represent[ed] the most significant departure from the traditional FDA standards for drug approval."[54] Subpart H's "major point of departure" from previously existing approval regimes was its focus on granting drug approval "on the basis of the drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit over time."[55] A "surrogate end point" or "surrogate marker" is "a laboratory parameter or physical sign that is used in a clinical trial as a substitute for a clinically meaningful end point, such as mortality."[56] The value of surrogate endpoints lies in their ability to predict clinical outcomes.[57] As "examples of surrogate end points that have been proven to be excellent predictors of clinical outcomes and, hence, have saved both money and precious time expediting drugs to the patient care arena," Dean Dennis Thompson cites "a diverse group of antihypertensive drugs approved on the basis of reduced blood pressure effects [that] has shown clear benefits in reducing cardiovascular events and mortality."[58] With the passage of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Congress effectively codified Section 314.510, the surrogate endpoint provision of Subpart H.[59]

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[50] *See Interim Rule*, "Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses," 53 Fed. Reg. 41,516 (Oct. 21, 1988). The Subpart E rules may be found at 21 C.F.R. §§ 312.80-88.

[51] *See* Greenberg, *infra* Appendix A, at 321.

[52] Greenberg, *infra* Appendix A, at 321 (citation omitted).

[53] Greenberg, *infra* Appendix A, at 323.

[54] Shulman and Brown, *infra* Appendix A, at 514.

[55] Shulman and Brown, *infra* Appendix A, at 514. Likewise, Greenberg observed that the "essential element of the accelerated approval regulations [*i.e.*, Subpart H] was the provision that 'surrogate endpoints' could be employed as the empirical basis for FDA approval of a new drug." Greenberg, *infra* Appendix A, at 323 (citation omitted).

[56] Dennis F. Thompson, "Surrogate End Points, Skepticism, and the CAST Study," editorial, *Annals of Pharmacotherapy*, 36 (Jan. 2002): 170-71, at 170 (citations omitted).

Neither Shulman and Brown nor Greenberg focused on a second type of drug approval included in Subpart H – codified now at 21 C.F.R. § 314.520.[60] This second avenue for Subpart H approval is reserved for circumstances in which "FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted."[61] Pursuant to this provision "FDA may approve a treatment subject to special distribution or use restrictions that address outstanding safety issues."[62] Section 314.520 balanced FDA's desire to bring clinically beneficial drugs to the market with the agency's concern that "[s]ome drugs, however, are so inherently toxic or otherwise potentially harmful that it is difficult to justify their unrestricted use."[63] The agency explained "that some clinically beneficial drugs can be used safely only if distribution and use are modified and restricted."[64]

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[57] *See* Thompson, *infra* Appendix A, at 170.

[58] Thompson, *infra* Appendix A, at 170.

[59] This codification was part of Congress's major reauthorization and modernization of the Federal Food, Drug & Cosmetic Act. Section 506(b) of FDAMA (21 U.S.C. § 356) "in effect, codifie[d] in statute FDA's Accelerated Approval Rule . . . , made final in 1992, which allows expedited marketing of certain new drugs or biological products intended to treat serious or life-threatening illnesses and that appear to provide meaningful therapeutic benefits to patients compared with existing treatments." FDA Centers for Drug Evaluation and Research and for Biologics Evaluation and Research, *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review*, at 2 (Sept. 1998) (footnote omitted). While clearly codifying Subpart H's surrogate endpoint provision at 21 U.S.C. § 356(b)(1), Congress does not appear to have enacted a parallel provision to Section 314.520, which pertains to "restricted use" drugs, under which Mifeprex was approved.

[60] Section 314.520 (Approval with restrictions to ensure safe use.) states:

> (a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the drug product, such as:
> (1) Distribution restricted to certain facilities or physicians with special training or experience; or
> (2) Distribution conditioned on the performance of specified medical procedures.
> (b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

[61] *Subpart H Final Rule*, 57 Fed. Reg. at 58942.

Section 314.520 is intended for drugs that are vitally necessary, but which may impose greater than normal risks for the patient.[65] FDA was willing "to approve such high risk drugs for early marketing if the agency can be assured that postmarketing restrictions will be in place to counterbalance the known safety concerns."[66] Postmarketing restrictions would be designed "to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction."[67] FDA intended to employ restrictions on distribution "only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will *not* assure the product's safe use."[68] In the absence of restrictions, which "may vary with the circumstances of each drug[,] . . . the drug would be adulterated under Section 501 of the act, misbranded under Section 502 of the act, or not shown to be safe under Section 505 of the act."[69] In short, "[w]ithout such restrictions, the drugs would not meet the statutory criteria, could not be approved for distribution, and would not be available for prescribing or dispensing."[70] Mifeprex was the third of four drugs approved pursuant to Section 314.520.[71]

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[62] Geoffrey M. Levitt, James N. Czaban, and Andrea S. Paterson, "Chapter 6: Human Drug Regulation" in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 200.

[63] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[64] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[65] Of course, "[v]irtually all drug[s] can be toxic to humans, and no drug is completely free of risk," but, as the seriousness of an illness and the effect of the drug on that illness increase, "the greater the acceptable risk from the drug." *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[66] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

[67] *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

[68] *Subpart H Final Rule*, 57 Fed. Reg. at 58952 (emphasis added).

[69] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

D. FDA'S APPROVAL OF MIFEPREX UNDER ITS ACCELERATED APPROVAL REGULATIONS (SUBPART H) WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

FDA's accelerated approval regulations (Subpart H) apply to certain new drug products "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)"[72] When it proposed Subpart H in 1992, FDA observed that the following types of illness would fall within the reach of Subpart H:

> The terms "serious" and "life-threatening" would be used as FDA has defined them in the past. The seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes. For example, inflammatory bowel disease,

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[70] *Subpart H Final Rule*, 57 Fed. Reg. at 58951. The agency continued: "The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases, approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing." *Id.* at 58951-52.

[71] On June 7, 2002, the drug Lotronex (alosetron hydrochloride) was reintroduced to the market after a *Supplemental* NDA was approved pursuant to Subpart H's redistricted distribution provision. *See* Letter, FDA/CDER, Florence Houn, M.D., Director, Office of Drug Evaluation III to Olivia Pinkett, Product Director, Regulatory Affairs, GlaxoSmithKline (June 7, 2002): at 1 ("This supplemental application, considered for approval under 21 CFR 314, Subpart H at your request, narrows the original approved indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks and provides for a risk management program. . . . You have indicated your agreement with approval under restricted conditions.").

[72] 21 C.F.R. § 314.500. The rule was amended in 1999 to remove the words "and antibiotic." *See* Conforming Regulations Regarding Removal of Section 507 of the Federal Food, Drug, and Cosmetic Act, *Final Rule*, 64 Fed. Reg. 396, 402 (Jan. 5, 1999).

> asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus, erythematosus, depression, psychoses, and many other diseases can be serious for certain populations or in some or all of their phases.[73]

According to FDA, the agency has approved 38 NDAs, including the Mifeprex application, under Subpart H.[74] Of these approvals, 20 were for the treatment of HIV and HIV-related diseases, nine were for the treatment of various cancers and their symptoms, four were for severe bacterial infections, one was for erythema nodosum leprosum (leprosy), one was for hypotension, and, finally, one was for the termination of unwanted pregnancies.[75]

Pregnancy, without major complications, is not a "serious or life-threatening illness" for purposes of Subpart H. It is, rather, a normal physiological state experienced by most females one or more times during their childbearing years, and it is rarely accompanied by complications that threaten the life of the mother or the child. Following delivery, almost all women return to a normal routine without disability. Thus, pregnancy is not the kind of exceptional circumstance that falls within the scope of Subpart H. The fact that the Mifeprex Regimen is intended for healthy women provides further evidence of this point.

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[73] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13235. In the *Subpart H Final Rule*, FDA asserted that "serious and life-threatening illnesses" would be readily identifiable: "FDA discussed the meaning of the terms 'serious' and 'life-threatening' in its final rules on 'treatment IND's' (52 FR 19466 at 19467, May 22, 1987) and 'subpart E' procedures (54 FR 41516 at 41518-41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every 'serious' and 'life-threatening' disease that would be within the scope of this rule. In FDA's experience with 'treatment IND's' and drugs covered by the 'subpart E' procedures there have not been problems in determining which diseases fall within the meaning of the terms 'serious' and 'life-threatening,' and FDA would expect no problems under this accelerated approval program." *Subpart H Final Rule*, 57 Fed. Reg. at 58945.

[74] These estimates are based on the version of FDA's webpage, dated February 5, 2002, listing Subpart H approvals, *infra* Appendix A.

[75] *See* FDA/CDER webpage, "NDAs Approved under Subpart H," *infra* Appendix A. A copy of the most recently available version is reproduced in Appendix C (available at: <http://www.fda.gov/cder/rdmt/accapp.htm>). *See also* "NDA Supplements Approved under Subpart H" (available at: <http://www.fda.gov/cder/rdmt/accappr1.htm>) (supplemental approvals are not included in the figures set forth in the text because they refer to FDA actions regarding drugs that have already been approved).

In fact, the Population Council argued strenuously that its application for mifepristone did not fall within the scope of Subpart H.[76] In a letter to FDA written approximately three weeks before the final approval of the mifepristone NDA, the Population Council's Sandra P. Arnold protested, ". . . it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider."[77] Arnold argued correctly that "[n]either pregnancy nor unwanted pregnancy is an illness, and Subpart H is therefore inapplicable for that reason alone."[78] She continued, stating, "Neither is pregnancy nor unwanted pregnancy a 'serious' or 'life-threatening' situation as that term is defined in Subpart H."[79] In the next paragraph, after directly quoting the *Supbart H Final Rule*, Ms. Arnold asserted that "[t]he plain meaning of these terms does not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy."[80] She added that, unlike HIV infection, pulmonary tuberculosis, cancer, and other illnesses, "pregnancy and unwanted pregnancy do not affect survival or day-to-day functioning as those terms are used in Subpart H."[81] She continued that, "although a pregnancy 'progresses,'" the development of a pregnancy "is hardly the same as the worsening of a disease that physicians call progression."[82]

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[76] The Population Council appears to have been concerned about getting the drug approved "without invoking the Subpart H regulatory provisions that signal 'big deal' to the pharmaceutical industry." Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 4 [FDA FOIA Release: MIF 001333-49]("Sandra Arnold Letter"). Sandra Arnold was "Vice President, Corporate Affairs" of the Population Council.

[77] Sandra Arnold Letter at 1.

[78] Sandra Arnold Letter at 1-2.

[79] Sandra Arnold Letter at 2.

[80] Sandra Arnold Letter at 2.

[81] Sandra Arnold Letter at 2.

[82] Sandra Arnold Letter at 2. Ms. Arnold also warned the agency that extending the scope of Subpart H to include pregnancy and unwanted pregnancy by exercising agency "judgment" was not defensible; the exercise of such judgment should go to whether or not "a particular disease actually is serious, not [act as] a means of stretching the meaning of serious to cover entirely new categories of non-serious situations." *Id.*

Additionally, Mifeprex fails to meet the second requirement set forth in Section 314.500 that drugs approved under Subpart H "provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)" As was noted above, the Mifeprex Approval Memo contends "that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H [and] [t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[83] By defining the "therapeutic benefit" solely as the avoidance of the current standard of care's delivery mechanism, FDA effectively guarantees that a drug will satisfy this second prong of Subpart H as long as it represents a different method of therapy.[84] It does not appear that such considerations formed the basis of any other Subpart H approval.

When FDA adopted Subpart H, it cited as "readily understood illustrations of the intent of the [meaningful therapeutic benefit] requirement" an "improved response compared to available therapy" and the "ability to treat unresponsive or intolerant patients."[85] Based on these illustrations, Mifeprex does not fall within the intent of the requirement. First, there is a less dangerous, more effective alternative to Mifeprex available for the termination of pregnancies: namely, surgical abortions. Dr. Jeffrey Jensen conducted a study to compare the safety and efficacy of medical abortion with that of surgical abortion.[86] The study compared 178 patients who, as participants in the U.S. clinical trial in support of the Mifeprex NDA, underwent mifepristone/misoprostol abortions, with 199 patients who later received surgical abortions at the same clinical site. The primary procedure failed (*i.e.*, there was a subsequent surgical intervention) in 18.3 percent of the mifepristone/misoprostol patients and 4.7 percent of the surgical patients.[87] Of the mifepristone/misoprostol patients who failed their primary procedure, 12.5 percent required surgical intervention for acute bleeding, 43.8 percent for persistent bleeding, 15.6 percent for incomplete abortion, and 28.1 percent for ongoing pregnancy.[88] By contrast, the sole cause for surgical intervention among the surgical patients who failed their primary procedure was persistent bleeding.[89] In addition, mifepristone/misoprostol patients "reported significantly longer bleeding" and "significantly higher levels of pain . . . , nausea . . . , vomiting . . . , and diarrhea" than their surgical counterparts.[90]

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[83] Mifeprex Approval Memo at 6.

[84] The view that merely making a different mode of therapy available *per se* produces a benefit is inconsistent with the position the agency has articulated elsewhere. MAPP 6020.3, which defines eligibility for FDA priority review, suggests that drug therapies are not inherently superior to non-drug therapies. Specifically, a drug may be afforded priority review if it would provide a significant improvement when compared with "marketed products . . . including non-"drug" products/therapies." *See* FDA/CDER, "Review Management: Priority Review Policy," MAPP 6020.3, at 1 (Apr. 22, 1996).

[85] *Subpart H Final Rule*, 57 Fed. Reg. at 58947.

Second, Mifeprex does not treat a subset of the female population that is unresponsive to, or intolerant of surgical abortion. To the contrary, because "medical abortion failures should be managed with surgical termination" the option for surgical abortion must be available for any Mifeprex patient.[91] As the U.S. trial conducted in support of the NDA indicated, the possibility for failure is substantial.[92] Thus, any patient who would be intolerant of surgical abortion, if such a class of patients exists, cannot use the Mifeprex Regimen.

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[86] Jeffrey T. Jensen, Susan J. Astley, Elizabeth Morgan, and Mark D. Nicols, "Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study," *Contraception* 59 (1999): 153-159 ("Jensen Study")[FDA FOIA Release: MIF 000438-44].

[87] *See* Jensen Study, *infra* Appendix A, at 155, Table 2.

[88] *See* Jensen Study, *infra* Appendix A, at 156, Table 3.

[89] *See* Jensen Study, *infra* Appendix A, at 156, Table 3.

[90] Jensen Study, *infra* Appendix A, at 156.

[91] Mifeprex Label ("Warnings").

As discussed below, FDA approved Mifeprex pursuant to Section 314.520 in order to impose safety restrictions to counteract the risks it had identified. FDA, confronted by the sponsor's refusal to establish voluntary restrictions on distribution,[93] viewed Subpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe.[94] The inappropriate application of Section 314.520 served the agency's immediate need of conditioning the drug's approval on certain safety measures. However, Mifeprex fails to satisfy the Subpart H requirements because, although it presents great risk to the user, it neither treats a serious or life-threatening illness nor provides a therapeutic benefit above existing treatments. A drug with such characteristics should not have been approved.

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[92] FDA, "Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments," at 11 (Table 1) (reporting a failure rate of 8% for pregnancies less than or equal to 49 days' duration) ("Medical Officer's Review").

[93] Early in the approval process, FDA anticipated that the Population Council would cooperate, thus obviating the need for Subpart H restrictions: "[B]ecause the applicant has voluntarily proposed a system of limited distribution, imposition of further distribution restrictions under the Agency's Subpart H regulations does not appear warranted." *See* Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62]. The voluntary restrictions placed on the drug Accutane, a drug for severe acne, illustrate that a cooperative drug sponsor may be able to obviate the need for Subpart H restrictions. Because Accutane can cause birth defects, the restrictions are designed to ensure that women taking the drug are not and do not become pregnant. The "System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™)," controls the distribution of the drug through the issuance of yellow Accutane Qualification Stickers. These stickers are distributed to physicians who meet a number of qualifications and they, in turn, distribute them to patients, who must undergo two tests to confirm they are not pregnant and must commit to use two forms of contraception. Pharmacists may fill prescriptions for the drug only if they bear the qualification sticker, were issued within the past week, and prescribe no more than 30 days' worth of the drug. *See* Accutane Label.

[94] This interpretation of the agency's actions is supported by FDA spokeswoman Crystal Rice, who said "that outside of Subpart H, the FDA does not have another regulatory program to mandate safety restrictions on drug marketing for drugs used to treat 'serious or life-threatening illnesses'" and "that 'other agreements [or restrictions on the drug] not under Subpart H worked out between FDA and a sponsor would be essentially voluntary.'" "Danco Medical Director Explains Mifepristone's FDA Approval Not Fast-Tracked or Accelerated, Despite Media Reports," *Kaiser Daily Reproductive Health Report* (March 29, 2001) (available at: <http://report.kff.org/archive/repro/2001/3/kr010329.5.htm>).

E. THE CLINICAL TRIALS DID NOT PRESENT "SUBSTANTIAL EVIDENCE" THAT THE MIFEPREX REGIMEN IS SAFE AND EFFECTIVE

FDA's approval of the Mifeprex NDA ran counter to Congress's statutory requirements, the agency's regulations and guidance documents, and FDA's well-established standards for the quality and quantity of scientific evidence needed to support an agency finding that a new drug is safe and effective. The clinical trials submitted by the Population Council to support its NDA did not use the full set of design features FDA typically requires to produce unbiased investigations of drug safety and effectiveness. Because these trials were not blinded, randomized, or concurrently controlled, they did not establish the safety and effectiveness of the Mifeprex Regimen. Inexplicably, FDA failed to perform a statistical analysis of the data from the American trial. Furthermore, FDA's approval of Mifeprex pursuant to Subpart H compounds the deficiencies in the trials because sponsors of Subpart H drugs must demonstrate that the drug for which approval is being sought provides a "meaningful therapeutic benefit over existing therapy." Because Mifeprex was approved in reliance on French and American trials that did not compare the Mifeprex Regimen with the existing standard of care for ending pregnancies (*i.e.*, surgical abortion), the trials cannot support this Subpart H approval.

1. The Clinical Trials Underlying FDA's Approval of Mifeprex

FDA based its approval of Mifeprex on safety and effectiveness data derived from two French clinical trials ("French Clinical Trials") and one U.S. clinical trial ("U.S. Clinical Trial").[95] Neither the French Clinical Trials nor the U.S. Clinical Trial was blinded, randomized, or concurrently controlled – the hallmarks of unbiased, scientific analysis generally relied upon by FDA.

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[95] *See* Mifeprex Approval Memo, *infra* Appendix A, at 1.

a. The French Clinical Trials

The French Clinical Trials, which formed the basis for the Population Council's original NDA submission in 1996, were open-label, multi-center studies.[96] One of these trials consisted of 1,286 patients at 24 centers in France ("French Trial I").[97] The trial was limited to women who had pregnancies of no more than 49 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.[98] On the first day of the procedure, the patient received 600 mg of mifepristone orally "in the presence of a study investigator."[99] Approximately 48 hours later, she returned and, unless the abortion had already taken place, ingested 400 micrograms of misoprostol "in the presence of a study investigator."[100] The patient remained under observation for four hours or more after the ingestion of misoprostol and returned for "a final assessment of the pregnancy termination procedure" eight to 15 days later.[101]

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[96] FDA's Reproductive Health Drugs Advisory Committee ("FDA Advisory Committee"), which met in July 1996 to consider the mifepristone NDA, based its conclusion primarily on the French trial along with preliminary data from the U.S. Clinical Trial. *See* FDA Advisory Committee, *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy*, at 6, 132-33 (July 19, 1996) (*FDA Hearings Transcript*)[FDA FOIA Release: MIF 005200-90]. Committee member Dr. Mary Jo O'Sullivan asked why the Committee meeting was being held "at this time when the data is not finalized." *Id.* at 37. Dr. C. Wayne Bardin, who was responsible for overseeing the Population Council's NDA preparation, responded that "we have sufficient data . . . [f]rom the non-U.S. data to allow us to submit an application to the FDA." *Id.*

[97] *See* FDA, Statistical Review and Evaluation, at 2-4 (May 21, 1996) ("Statistical Review"). This French trial is referred to as FFR/91/486/14.

[98] *See* Statistical Review, *infra* Appendix A, at 2. "Since the ultrasound estimate of gestational age was more reliable than the patient's estimate . . . gestational age based on the ultrasound examination was used if available." *Id.* Investigators, in violation of study protocol, included some women with pregnancies of more than 49 days. *See* Statistical Review, *infra* Appendix A, at 3.

[99] *See* Statistical Review, *infra* Appendix A, at 2.

[100] *See* Statistical Review, *infra* Appendix A, at 2.

[101] *See* Statistical Review, *infra* Appendix A, at 2.

The efficacy analysis of French Trial I encompassed only 1,205 patients, while the safety analysis included all 1,286 participants.[102] The regimen resulted in "complete expulsion" in 95.4 percent of the 1,189 participants whose pregnancies were 49 days or less.[103] The rate of complete expulsion declined with increased gestational age.[104] Sixty-one women had complete expulsions before taking misoprostol.[105] Almost 86 percent of patients in French Trial I experienced at least one adverse event as a result of the procedure.[106]

The second French clinical trial ("French Trial II") enrolled 1,194 patients at 11 centers.[107] The trial was limited to women who had pregnancies of no more than 63 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.[108] The regimen used in French Study II was essentially the same as that described above in connection with French Study I, except that an additional 200 micrograms of misoprostol was administered if complete expulsion did not occur within three hours after taking the initial 400 microgram dose of misoprostol.[109] Patients who received the second dose of misoprostol remained under observation for a total of five hours.[110]

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[102] *See* Statistical Review, *infra* Appendix A, at 3.

[103] *See* Statistical Review, *infra* Appendix A, at 3. Patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (2.8%), ongoing pregnancies (1.5%), and those who needed surgical procedures for bleeding (.3%) were classified as failures. *See id.* at 3 and 9 (Table 1).

[104] *See* Statistical Review, *infra* Appendix A, at 3 ("[T]here was a statistically significant . . . inverse relationship between gestational age and the success rate as the success rate generally declined with increasing gestational age.").

[105] *See* Statistical Review, *infra* Appendix A, at 3. Twenty-six of these women received misoprostol anyway, because the investigators did not realize that they had had complete abortions. *See id.*

[106] *See* Statistical Review, *infra* Appendix A, at 4.

[107] *See* Statistical Review, *infra* Appendix A, at 4-7. This French trial is designated as FF/92/486/24.

[108] *See* Statistical Review, *infra* Appendix A, at 4-5.

[109] *See* Statistical Review, *infra* Appendix A, at 5.

[110] *See* Statistical Review, *infra* Appendix A, at 5.

The efficacy analysis of French Trial II encompassed only 1,104 patients, while the safety analysis included all 1,194 participants.[111] The regimen resulted in "complete expulsion" in 92.8 percent of the participants.[112] The rate of complete expulsion declined with increased gestational age.[113] Twenty-six women had complete expulsions before taking misoprostol.[114] Almost 93 percent of patients in French Trial II experienced at least one adverse event as a result of the procedure.[115]

Among the deficiencies that characterized both French Clinical Trials was the absence of an appropriate control group. Consequently, as an FDA statistician concluded after reviewing the data from the French Clinical Trials: "In the absence of a concurrent control group in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy."[116]

b. The U.S Clinical Trial

The U.S. Clinical Trial was carried out from September 13, 1994 to September 12, 1995 at various qualified university hospitals and clinics.[117] Patients had to satisfy a number of criteria to be included in the study.[118] All patients were screened by pelvic examination and ultrasound to ensure that their pregnancies were not too advanced for the procedure.[119] On their first visit, patients took 200 mg of mifepristone orally "[i]n the presence of the investigator."[120] Patients returned 36 to 60 hours later to ingest 400 micrograms of misoprostol orally in the presence of the investigator, unless the investigator determined that the termination was already complete.[121] Following ingestion of misoprostol, patients were observed for a minimum of four hours.[122] Patients were instructed to return again 12 days later for a follow-up assessment.[123] A patient's pregnancy was terminated surgically "at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion."[124]

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[111] *See* Statistical Review, *infra* Appendix A, at 5.

[112] *See* Statistical Review, *infra* Appendix A, at 6. As in French Study I, patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (4.0%), ongoing pregnancies (2.3%), and those who needed surgical procedures for bleeding (.9%) were classified as failures. *See id.* at 5 and 12 (Table 4).

[113] *See* Statistical Review, *infra* Appendix A, at 6.

[114] *See* Statistical Review, *infra* Appendix A, at 6.

[115] *See* Statistical Review, *infra* Appendix A, at 7.

[116] Statistical Review, *infra* Appendix A, at 7-8.

[117] *See* Medical Officer's Review, *infra* Appendix A, at 6. More specifically, the U.S. Clinical Trial consisted of "two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols." Medical Officer's Review, *infra* Appendix A, at 6 and 9. In this Petition, the trials will be referred to as "the U.S. Clinical Trial," because the protocols employed were identical, the results of the two trials were analyzed jointly, and the results were published in the same article. *See* Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri

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Benton, M.D., and Ann Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," *New England Journal of Medicine* 338 (Apr. 30, 1998): 1241-47 ("Spitz Article") ")[FDA FOIA Release: MIF 006692-97]. The members of the FDA Advisory Committee who were still working for FDA at the time of publication received a copy of the Spitz Article. *See* Medical Officer's Review, *infra* Appendix A, at 29. Although FDA considered data from the entire U.S. Clinical Trial, it appears that the agency formally approved Mifeprex based only on the portion of the U.S. Clinical Trial data that was generated among women whose pregnancies were no more than 49 days' gestational age. *See* Mifeprex Approval Memo, *infra* Appendix A, at 1 ("The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period."). *See also* Mifeprex Label ("Clinical Studies").

[118] Among the inclusion criteria were requirements that a patient be at least 18 years old, be in good health, have an intrauterine pregnancy of no more than 63 days (confirmed by a pelvic examination *and* ultrasound), and have agreed to a surgical abortion if the mifepristone-misoprostol abortion failed. Medical Officer's Review, *infra* Appendix A, at 7-8. The study excluded women with certain health problems, such as liver, respiratory, or renal disease, cardiovascular disease, chronic hypertension, anemia, clotting problems, pelvic inflammatory disease, and ectopic pregnancies. *See id.* at 8. In addition, women who were over 35 and smoked, had IUDs, were breastfeeding, were unlikely to comply with study requirements, or who "[l]ived or worked more than one hour from the emergency care facility" were excluded. *See id.* at 8-9.

[119] *See* Medical Officer's Review, *infra* Appendix A, at 8.

[120] Medical Officer's Review, *infra* Appendix A, at 9.

[121] *See* Medical Officer's Review, *infra* Appendix A, at 9.

[122] *See* Medical Officer's Review, *infra* Appendix A, at 7.

[123] *See* Medical Officer's Review, *infra* Appendix A, at 7.

[124] Medical Officer's Review, *infra* Appendix A, at 16.

The U.S. Clinical Trial consisted of 2,121 subjects.[125] Of these patients, 2,015 were evaluated for efficacy,[126] which "was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure."[127] The remaining 106 patients did not return for the third visit.[128] The mifepristone-misoprostol combination was effective in 92 percent of patients with pregnancies no greater than 49 days, 83 percent of patients with pregnancies between 50 and 56 days, and 77 percent of women with pregnancies between 57 and 63 days.[129] All 2,121 subjects were evaluated for safety.[130] Ninety-nine percent of patients experienced adverse events and most of these experienced multiple adverse events.[131] Twenty-three percent of the adverse effects experienced by each gestational age group were "severe."[132]

Finally, FDA did not conduct a statistical review of the results of the U.S. Clinical Trial. FDA's statistical reviewer explained this failure by noting that "[a] statistical evaluation of the European studies was completed previously "and "[t]he clinical results of the supporting U.S.

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[125] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[126] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[127] Medical Officer's Review, *infra* Appendix A, at 16. The failure to establish a pre-trial, statistical definition for drug efficacy was a defect in trial design.

[128] *See* Medical Officer's Review, *infra* Appendix A, at 16. It would have been appropriate to include these 106 patients in the efficacy analysis as "failures," if for no other reason than that they did not appear for all three required visits. Although "[f]or 92 of these patients, there was some information suggesting a successful outcome," *id.* at 10, there was neither definitive evidence of complete abortion nor, apparently, any information with respect to whether these women subsequently experienced any adverse effects. In fact, during their second visit, five of these 106 women were diagnosed as having continuing pregnancies. *Id.* at 10. *See also* Spitz Article, *infra* Appendix A, at 1246 ("The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women.").

[129] *See* Medical Officer's Review, *infra* Appendix A, at 11 (Table 1).

[130] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[131] *See* Medical Officer's Review, *infra* Appendix A, at 11.

[132] *See* Medical Officer's Review, *infra* Appendix A, at 11.

studies . . . are similar enough to the results of the European studies that, in the opinion of the medical reviewer, a statistical evaluation of the results of the U.S. studies is not required."[133]

2. Requirements for Proving Drug Safety and Effectiveness

FDA has developed a rigorous default standard for scientific demonstrations of safety and effectiveness of human drug products.[134] Section 505(d)(5) of the FD & C Act provides, in relevant part, that FDA shall refuse to approve a new drug application when "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[135] Section 505(d) defines "substantial evidence" to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . ."[136] FDA has stated that "substantial evidence" requires a showing of clinically significant evidence of effectiveness rather than mere statistical evidence of significance.[137] No such showing was made for Mifeprex, which has been demonstrated to be less effective than surgical abortion for all segments of the population.

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[133] FDA, "Statistical Comments on Amendment 024," Memorandum to File NDA 20-687 (Feb. 14, 2000). This document is available along with the agency's Statistical Review. *See* Statistical Review, *infra* Appendix A.

[134] *See* the discussion of the development and requirements of FDA's "gold standard," *supra* Section III.C.1.

[135] 21 U.S.C. § 355(d)(5).

[136] 21 U.S.C. § 355(d) ("the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.").

[137] *See Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 155 (D.C. Cir. 1986) ("It is important to note that the Commissioner does not contend that the effectiveness shown must amount to a 'medical breakthrough', as ARW complains, but contends in his brief that he would be satisfied with even a modest clinical or therapeutic effect.").

Section 314.126 of FDA's rules states that "[r]eports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs."[138] The rule states that a major purpose of an adequate and well-designed study is to "permit[ ] a valid comparison with a control to provide a quantitative assessment of drug effect."[139] According to Section 314.126(b), an adequate and well-controlled study serves to ensure that the subjects of the trial have the disease or condition being studied,[140] that the method of assigning patients to treatment and control groups minimizes bias (*e.g.*, using randomization),[141] and, that "[a]dequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data" (*e.g.*, blinding).[142] The criteria that the rule establishes "have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation."[143]

Agency guidance provides that FDA may approve an NDA based on only one, not two, effectiveness trials for drugs in one of the following three categories:

> 1) when effectiveness may be demonstrated adequately with existing studies of another claim or dose (e.g., approval for pediatric use on the basis of studies in adults); 2) when a controlled trial of a specific new use is supported by evidence from adequately controlled trials from related uses, dosages, or endpoints; and 3) when a single multicenter trial provides statistically convincing and clinically meaningful evidence of effectiveness, supported by confirmatory research.[144]

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[138] 21 C.F.R. § 314.126(a) ("Adequate and well-controlled studies.").

[139] 21 C.F.R. § 314.126(b)(2) (describing "placebo concurrent control," "dose-comparison concurrent control," "no treatment concurrent control," "active treatment concurrent control," and "historical control").

[140] 21 C F.R. § 314.126(b)(3).

[141] 21 C F R. § 314.126(b)(4).

[142] 21 C.F.R. § 314.126(b)(5).

[143] 21 C.F.R. § 314.126(a).

[144] Kulynych, *infra* Appendix A, at 146 (citing FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) at 5-17 (*FDA Effectiveness Guidance*).

Mifepristone did not fall within any of these categories. The first and second categories were inapposite because mifepristone had not been approved for any use in any population in the United States; additionally, no evidence from adequate and well-controlled trials had ever been presented to FDA regarding any use for mifepristone. Because neither the French Clinical Trials nor the U.S. Clinical Trial was randomized, blinded,[145] or comparator-controlled, none of these trials could provide the type of data necessary for the third category either. Furthermore, these studies lacked "clear, prospectively determined clinical and statistical analytic criteria."[146]

Even though FDA takes the position elsewhere that the extent to which a trial's design controls for various types of bias "is a critical determinant of its quality and persuasiveness,"[147] neither the French Clinical Trials nor the U.S. Clinical Trial were randomized, concurrently controlled, or blinded. A control group "allow[s for] discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment."[148] Control groups also enable investigators to determine "what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective."[149]

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[145] Blinding is the normal method by which those who evaluate a medication's effectiveness and side effects, are kept unaware of whether they are evaluating the comparator drug (sometimes a placebo), or the new medication (or procedure) under study. If possible, the patient is also blinded and not allowed to know which treatment she is receiving ("double-blinding"). According to standard scientific and medical practice and the standards to which FDA holds pharmaceutical sponsors, all clinical research studies investigating the effects of new drugs should be subjected to an assessment by a blinded evaluator. Conducting a concurrently-controlled, randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable. There are study designs that would have also allowed for blinding. Had blinding proved too difficult to perform, the requirement could have been waived based upon a satisfactory showing by the sponsor.

[146] *FDA Effectiveness Guidance*, *infra* Appendix A, at 12.

[147] FDA, "Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials," (Rockville, Md.: May 2001) at 3 (§ 1.2.1) (*FDA Guidance (ICH: E10): Choice of Control Group*). FDA's publication of "E10" is available at: <http://www.fda.gov/cder/guidance/4155fnl.pdf>.

[148] *FDA Guidance (ICH: E10): Choice of Control Group*, *infra* Appendix A, at 3 (§ 1.2) (Introduction, "Purpose of Control Group").

A trial that employs a concurrent control group drawn from the same population yields the most robust data. Concurrent control groups are chosen from the same population as the test group and are "treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time."[150] When concurrent control groups are used, the treatment and non-treatment groups are similar in all baseline and non-treatment variables that could influence the outcome or introduce bias into the study.[151]

By contrast, in a trial using external or historical controls "the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent; i.e., there is no concurrently randomized control group."[152] FDA cautions:

> "The external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome). Use of the latter comparator is particularly treacherous (such trials are usually considered uncontrolled) because general impressions are so often inaccurate."[153]

In such a trial, "[t]he control group is thus not derived from exactly the same population as the treated population."[154] If, as is most common, the external control group is composed of "a well-documented population of patients observed at an earlier time," the trial is said to be

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[149] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2).

[150] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2).

[151] *See FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2). "Bias here . . . means the systematic tendency of any aspects of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value." *Id.*

[152] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1).

[153] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 5 (§ 1.3.5).

[154] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1).

"historically" controlled.[155] Blinding and randomization are also not available to minimize bias when external or historical controls are used.[156]

According to FDA, the "[i]nability to control bias is the major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable."[157] A legal commentator recently cautioned courts about the scientific validity of experiments and trials that have no concurrent control.[158] She explained that "historically controlled subjects have not been subjected to exactly the same conditions as the test subjects."[159] Consequently, "one must be wary of" non-concurrently controlled studies (*i.e.*, historical, external, or uncontrolled studies) because their conclusions can be manipulated more easily than if concurrent controls are used.[160]

3. FDA's Acceptance of the French and U.S. Clinical Trial Data Violated Section 314.126(e) of the Agency's Rules

Section 314.126(e) of FDA's rules states unequivocally that "[u]ncontrolled studies or partially controlled studies *are not acceptable* as the *sole* basis for the approval of claims of effectiveness."[161] The section authorizes the use of uncontrolled trials merely to present supporting evidence for controlled trials; uncontrolled trials, if they are "carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug."[162]

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[155] *See FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1) ("but it could be a group at another institution observed contemporaneously, or even a group at the same institution but outside the study.").

[156] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 27 (§ 2.5.2).

[157] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.2).

[158] Erica Beecher-Monas, "The Heuristics of Intellectual Due Process: A Primer for Triers of Science," *New York University Law Review* 75: 1563-1657, 1628.

[159] Beecher-Monas, *infra* Appendix A, at 1628, n.357.

[160] Beecher-Monas, *infra* Appendix A, at 1628, n.357 (" 'you can prove anything with selective controls,' so one must be wary of historical controls," Beecher-Monas quoting Jon Cohen, "Cancer Vaccines Get a Shot in the Arm," 262 Science 841, 843 (1993)).

[161] 21 C.F.R. § 314.126(e)(emphasis added).

FDA recognizes a limited role for external, historically controlled studies. The agency takes the position that "[h]istorical (external) controls can be justified in some cases, but particular care is important to minimize the likelihood of erroneous inference."[163] Similarly, Section 314.126 cautions that "[b]ecause historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent controlled populations, historical control designs are usually reserved for special circumstances."[164] FDA cites as an example, "studies of diseases with high and predictable mortality (for example, certain malignancies),"[165] in which a decision might be made to offer all trial participants a potentially effective drug. Externally controlled studies also may suffice because "the effect of the drug is self-evident (general anesthetics, drug metabolism)."[166]

The French and U.S. Clinical Trials, which did not employ either external or historical control groups, were uncontrolled. During the Advisory Committee Hearings, FDA's Dr. Ridgley C. Bennett, who summarized the data from the French Clinical Trials, stated:

> There are very few studies comparing medical methods and vacuum aspiration for termination of early pregnancy. To date, no large randomized controlled trials have compared mifepristone plus misoprostol with suction curettage abortion. However, large published series have demonstrated morbidity rates associated with mifepristone plus prostaglandin to be similar to those of suction-curettage.[167]

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[162] 21 C.F.R. § 314.126(e).

[163] *FDA Guidance (ICH: E8): General Considerations, infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.2.2.2). According to FDA guidance, the "main advantage" of an externally controlled trial "is that all patients can receive a promising drug, making the study more attractive to patients and physicians." *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 27 (§ 2.5.6).

[164] 21 C.F.R. § 314.126(b)(2)(v) ("Historical control.").

[165] 21 C.F.R. § 314.126(b)(2)(v).

[166] 21 C.F.R. § 314.126(b)(2)(v).

[167] FDA Hearings Transcript, *infra* Appendix A, at 130. Jensen and his fellow researchers conducted "[a] prospective, noncurrent, single center cohort comparison." *See* Jensen Study, *infra* Appendix A, at 153. The study

"Published series" and uncontrolled studies cannot serve as a substitute for the well-controlled clinical trials that FDA requires. A concurrent control group would have been feasible because the trial participants were prepared to receive surgical abortion in the event of a failed mifepristone abortion.

The unusual circumstances that sometimes justify relying on externally controlled trials are not applicable with respect to pregnancy termination, generally, or the termination using mifepristone and misoprostol, specifically. Randomized, concurrently-controlled, blinded trials would have allowed investigators to compare not only the relative rates of complete termination and expulsion, but also the nature, intensity, and duration of the numerous side effects. In the absence of concurrent controls and blinding, the duration and intensity of cramping, nausea, bleeding, pain, and any emotional or psychological effects of the treatments would be subject to investigator and patient bias. The design of the U.S. Clinical Trial precluded unbiased comparison groups that could have helped analysts arrive "at a complete understanding of potential advantages, disadvantages and differences" between medical and surgical abortion.[168] FDA's *de facto* waiver of Section 314.126(e) constituted a gross departure from its past practice and announced standards for the conduct of adequate and well-controlled clinical trials.[169]

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compared the data from Mifeprex patients at one of the sites that participated in the U.S. Clinical Trial with data from patients who subsequently underwent surgical abortions at the same site. Although the methodological quality of this study is arguably superior to either the French or U.S. Clinical Trials, had it been offered as trial data it also would have been a weak substitute for a randomized controlled trial establishing equivalent or superior efficacy to surgical abortion.

[168] *See* Jensen Study, *infra* Appendix A, at 156. Dr. Cassandra Henderson, a member of the FDA Advisory Committee, wondered about this point as well: "Since this regimen is not without any side effects and we know that spontaneous abortion is not an infrequent occurrence, is it appropriate to use historical controls in trying to evaluate the efficacy of this regimen and not a randomized placebo trial?" FDA Hearings Transcript, *infra* Appendix A, at 131 (FDA's Dr. Ridgely C. Bennett gave the following puzzling response: "Well, I think it would be difficult to do a randomized trial of this nature. But I think it is fair to use a historical control for efficacy.").

[169] There is no evidence that FDA formally issued a waiver under Section 314.126(c) of the requirement for well-controlled studies or that the Population Council ever requested such a waiver.

4. Subpart H's Standard for Proving Drug Effectiveness

The approval of a drug under Subpart H does not lower the applicable standards for proving the drug's effectiveness. As FDA stated when it adopted Subpart H, "[a]ll drugs approved [under Subpart H] will have had effectiveness demonstrated on the basis of adequate and well-controlled studies."[170] In fact, Subpart H is available only for drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients *over existing treatments* (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."[171] Neither the French nor the U.S. Clinical Trials yielded scientifically valid comparisons with the existing therapy, surgical abortion, to support a finding of a "meaningful therapeutic benefit over existing treatments." FDA should have required the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone has a meaningful therapeutic benefit over the standard method for terminating pregnancies. FDA did not require the drug sponsor to perform such trials for Mifeprex, which departs from FDA's normal treatment of Subpart H drugs generally and for the other drugs approved under the restricted distribution provisions in Section 314.520.

Mifeprex appears to be the only drug that FDA has approved under Section 314.520 of Subpart H without requiring compliance with the statutory and regulatory requirements that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials capable of providing data for subjection to rigorous statistical analysis.

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[170] *Subpart H Final Rule*, 57 Fed. Reg. at 58953.

[171] 21 C.F.R. § 314.500 (emphasis added). The class of "existing treatments" to which there must be a comparison, as specified in this rule section, is not limited to pharmaceuticals. For example, a potential chemotherapeutic agent might be compared to radiation therapy.

Aside from Mifeprex, only four drugs have been approved pursuant to Section 314.520, the restricted distribution prong of Subpart H. Each of these drugs, Xeloda,[172] Thalomid,[173] Actiq,[174] and Tracleer,[175] was an appropriate candidate for approval under Section 314.520. Moreover, in each case, studies were performed that allowed for a meaningful statistical analysis of the effectiveness of this drug in comparison with the current available standard of care. FDA's decision to require randomized, comparator-controlled, blinded trial design for each drug, even in the face of urgent need for the treatments at issue, supports the claim that FDA's treatment of the mifepristone NDA was aberrant.

Xeloda™ (capecitabine) was approved for use in treating patients with widely metastatic ("Stage IV") terminal breast cancer, for whom all other modalities of chemotherapy have failed or are contraindicated.[176] The average lifespan of a patient with multi-drug resistant tumors participating in the clinical trials for this drug was only 8.5 months. Because Xeloda was only modestly effective (25% of the recipients improved for an average of five months), exhibited significant toxicity, and was a last resort treatment for dying patients, FDA approved it under Section 314.520 with use restrictions and commitments to further study the drug. Subsequent randomized, concurrent controlled, blinded evaluator trials demonstrated Xeloda's statistical superiority to the standard of care for metastatic colon and breast cancers.[177]

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[172] NDA 20896.

[173] NDA 20785.

[174] NDA 20747.

[175] NDA 21290.

[176] *See* "NDAs Approved under Subpart H," *infra* Appendix A. The current version of the Subpart H approval chart (updated Aug. 8, 2002) indicates that Xeloda is a "surrogate endpoint" drug, rather than a restricted distribution drug. However, the two previous postings of the chart state the opposite. Furthermore, FDA's approval letter states that the NDA "[was] approved under 21 CFR 314.520." Letter, FDA/CDER to Cynthia Dinella, Group Director, Regulatory Affairs, Hoffman-La Roche Inc. (Apr. 30, 1998).

[177] *See* Xeloda package insert.

Thalidomide (Thalomid™) was approved under Section 314.520 for the treatment of leprosy, a disfiguring, chronically disabling, and often lethal skin infection.[178] Thalidomide is a drug the severe toxicity of which, particularly to fetuses, is well-documented. Children exposed to this drug *in utero* suffer dramatic birth defects, namely the partial absence of hands, feet, arms and legs. The public outcry following the discovery that thalidomide causes these alarming malformations helped to spur the scientific modernization of FDA drug approval policy and practices in the 1960s. Clinical trials involving leprosy are difficult and require long periods of time because the disease is very rare in the United States. Three randomized, double-blinded comparator-controlled clinical trials were performed to support the Thalomid NDA.[179]

Oral fentanyl citrate (Actiq™) was approved under Section 314.520 as a powerful sedating narcotic painkiller, primarily for use to relieve the suffering of dying cancer patients.[180] Actiq can be lethal, particularly to children, because it quickly abolishes a patient's drive to breathe, unless the patient is already accustomed to narcotic analgesics. Moreover, Actiq, a powerful narcotic, has a high potential for abuse and diversion into the illegal drug market. Actiq was evaluated in a "double blinded, placebo controlled" study for the treatment of breakthrough cancer pain and was shown to "produce statistically significantly more pain relief compared with placebo."[181] Actiq is restricted for use only by oncologists and pain specialists who are familiar with the management of the side effects and complications of the drug's use as approved.

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[178] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[179] *See* Thalomid package insert.

[180] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[181] Actiq package insert.

Tracleer™ (bosentan tablets) was approved pursuant to Section 314.520 for use in treating pulmonary hypertension, a life threatening and frequently progressive condition of excessively high blood pressure in the lung blood vessels resulting from chronic scarring and injury of the lung tissue.[182] Tracleer can cause liver damage and major birth defects. Two randomized, double-blinded, placebo-controlled clinical trials demonstrated the superiority of the drug over a placebo. Tracleer was compared to a placebo because there is no alternate standard of care for pulmonary hypertension. Despite its potential toxicity, Tracleer was approved subject to usage restrictions under Section 314.520 because it is the only treatment available for a life threatening and debilitating condition.[183]

5. FDA Failed to Require a Comprehensive Audit of French Clinical Trial Data after Discovering Violations of Good Clinical Practices

In June 1996, FDA inspected the trial records of a "French government-supported abortion clinic" that participated in the French Clinical Trials. FDA issued a Form 483 detailing problems uncovered during the inspection. The problems identified by the investigator suggested carelessness, fraud, evidence tampering, and the systematic under-reporting of serious adverse events. The inspection "revealed a failure to maintain complete and accurate records." The violations that were discovered included: "laboratory reports that were missing" for 11 patients, "missing ultrasound documents" for 20 patients, "pages missing from the case record files and unreported aspirations," inclusion of 4 ineligible patients, and "consent forms were dated after the start of study for some subjects, and the investigator had signed consent form sometimes in advance, up to 4 days before the subjects had signed."[184] There were also "under-reported side effects" such as "a patient bleeding with two subsequent aspirations; convulsions reported as fainting; and expulsion which was actually a surgical evacuation; bleeding, nausea and contractions, or bleeding and pelvic pain."[185] After elaborating on the deficiencies found, the FDA inspector concluded: "Notwithstanding these objectionable conditions, [redacted name of an FDA official] assured Dr. Aubeny that he would not recommend that the studies not be included in the evaluation of the NDA application."[186]

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[182] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[183] *See* Tracleer package insert.

FDA should not have allowed tainted data to support the Mifeprex NDA. A complete audit of all French Clinical Trial data is warranted to determine whether another set of clinical trials must be performed to replace the tainted French trial data.

F. THE AGENCY'S DE FACTO APPROVAL OF MISOPROSTOL'S NEW USE WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

When FDA approved Mifeprex, it also took action with respect to a second drug – misoprostol. Taken alone, mifepristone is ineffective as an abortifacient.[187] In order to achieve an abortion rate greater than 90 percent, the administration of mifepristone is followed approximately two days later by a prostaglandin to complete the abortion. In the U.S. Clinical

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[184] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1 [FDA FOIA Release: MIF 004135-45].

[185] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1.

[186] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 9.

[187] Although some studies using mifepristone alone have produced completion rates as high as 60 to 80 percent, it is widely recognized that, on its own, mifepristone is not a viable substitute for surgical abortion. *See, e.g.,* Mitchell D. Creinin, "Early Medical Abortion with Mifepristone or Methotrexate: Overview," *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 3 (reporting that "[f]or gestations up to 49 days, complete abortion occurs in approximately 60% to 80%" of women using mifepristone alone); Helena von Hertzen, M.D., "Research on Regimens for Early Medical Abortion," *Journal of the American Medical Women's Association* 55 (Supplement 2000): 133-36.

Trial, the prostaglandin used was misoprostol, which was distributed by G.D Searle & Co. ("Searle") as the anti-ulcer drug Cytotec™.[188] Ultimately, FDA based its approval of Mifeprex on the combined action of a mifepristone and misoprostol regimen. On the day FDA approved mifepristone, it notified Searle that "[t]he drug mifepristone is now approved in a regimen with misoprostol for termination of pregnancy of 49 days or less."[189]

Searle, which opposed the use of its drug in conjunction with Mifeprex as an abortifacient,[190] did not file a Supplemental NDA for the use of misoprostol as part of an abortion regimen.[191] Absent such an application, FDA lacked the basis for sanctioning a new indication for misoprostol. As Peter Barton Hutt, former FDA general counsel, observed, the agency's treatment of misoprostol "set[ ] an extraordinary precedent" because FDA was "seemingly encouraging a drug's unapproved use."[192] He added that the agency is in an "embarrassing and uncomfortable position."[193] FDA did more than encourage the unapproved use of misoprostol; it *mandated* the unapproved use.

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[188] After a series of corporate transactions, Searle is now part of Pharmacia Corporation, which is headquartered in Peapack, New Jersey. In 1985, G.D. Searle & Co. became the pharmaceutical unit of Monsanto. In April 2000, Monsanto merged with Pharmacia & Upjohn to create the Pharmacia Corporation. Pharmacia & Upjohn had been created in 1995 when Pharmacia AB and the Upjohn Company merged. On July 15, 2002, Pfizer Inc. announced that it would purchase Pharmacia.

[189] Letter, Dr. Lilia Talarico, M.D., Director, FDA/CDER, Division of Gastrointestinal and Coagulation Drug Products, Office of Drug Evaluation III to Dr. Mary Jo Pritza, G.D. Searle & Co. (Sept. 28, 2000): at 1 [FDA FOIA Release: MIF 008847-48]. The Talarico Letter came in response to the August 8, 2000 application by Searle to obtain approval for changes that would have bolstered the Cytotec label's discussion of adverse effects (presumably in anticipation of FDA's approval of the mifepristone NDA). FDA chided Searle for attempting to make the proposed changes and summarily rejected them. *Id.* at 1. When it announced the Mifeprex approval, FDA referred to the "approved treatment regimen." *See* FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000). *See also* FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 4 (referring to the "mifepristone treatment regimen").

[190] In fact, on August 23, 2000, Searle wrote an open letter to all health care practitioners stating that "Cytotec is not approved for the induction of labor or abortion." The letter listed a number of potential "[s]erious adverse events reported following off-label use of Cytotec in pregnant women includ[ing] maternal or fetal death." Michael Cullen, M.D., Medical Director U.S., Searle, Open Letter to Health Care Providers (Aug. 23, 2000)[FDA FOIA Release: MIF 008022]. Officials of the American College of Obstetricians and Gynecologists, among others, decried Searle's lack of cooperation. *See* Ralph W. Hale, M.D., and Stanley Zinberg, M.D., "The Use of Misoprostol in Pregnancy," editorial, *New England Journal of Medicine* 344 (Jan. 4, 2001): 59-60. FDA's approval of the Mifeprex Regimen in the face of Searle's opposition appears to have usurped Searle's rights to control the distribution of its drug.

[191] Because Searle's patent on misoprostol did not expire until July 2000, no other party would have been able to file a timely supplemental NDA for the use of a generic form of misoprostol as an abortifacient.

1. Misoprostol's Use as an Abortifacient is a New Indication for which the Requisite Supplemental New Drug Application Was Not Filed

A drug that differs in any material way (including in composition, effect, or intended use) from an approved drug is a new drug that must independently be established to be safe and effective.[194] Furthermore, a drug already being used to treat one disease or part of the body may be a new drug when used to treat another disease or part of the body.[195] Misoprostol's new use as an abortifacient, therefore, marks it as a "new drug."[196]

New drugs must be shown to be safe and effective. Specifically, FDA requires that "[a]ll indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) . . . unless the requirement is waived . . . ."[197]

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[192] Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1.

[193] Zimmerman at B1.

[194] *See Thompson v. Western Medical Center*, Brief for the Petitioners (filed by the Solicitor General of the United States), No. 01-344 (Dec. 2001): at 4 ("See *United States v. Generix Drug Corp.*, 460 U.S. 453, 460-461 (1983) (determination whether a product is a new drug takes into account both active and inactive ingredients); 21 C.F.R. 310.3(h) (discussing factors that make a drug a 'new drug').

[195] A drug may be deemed "new" because of "[t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4).

[196] The "newness" of misoprostol in this indication was heightened by the fact that, when Mifeprex was approved, misoprostol was explicitly contraindicated for pregnant women. The misoprostol label included the following black-box warning: "CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT . . . ." In April 2002, the Cytotec label was changed to "remove[ ] the contraindication and precaution that Cytotec should not be used in women who are pregnant." FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). The label now restricts the contraindication to pregnant women who are using Cytotec as a non-steroidal anti-inflammatory drug ("NSAID"). The revised Cytotec label and, more specifically, the "Indications and Usage" section, however, continue to lack any reference to the use of misoprostol in the Mifeprex Regimen.

[197] 21 C.F.R. § 201.57(c)(2). To the best of the Petitioners' knowledge, FDA did not formally waive the requirement for misoprostol as part of an abortion regimen.

A Supplemental NDA provides the necessary evidence in support of a new indication.[198] Absent a waiver, a Supplemental NDA permits FDA to consider the evidence in support of the proposed change and approve related labeling changes in advance.[199] Even though a new use for misoprostol is an integral part of the Mifeprex Regimen, FDA sanctioned this new misoprostol indication without having received and considered a Supplemental NDA.

Among the changes for which FDA approval is necessary are changes to statements in a drug's labeling indicating whether "[t]he drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy."[200] A well-known treatment regimen illustrates how FDA has typically dealt with the labeling of two drugs that have been approved for combined use. The regimen pairs methotrexate and Leucovorin Rescue. Methotrexate, a chemotherapeutic agent, kills cancer cells by depriving them of folic acid which is necessary for DNA synthesis, but, in the process, methotrexate deprives normal bone marrow cells of the folic acid they need. Leucovorin Rescue serves as an antidote to the toxic effects of methotrexate. The labeling for Leucovorin Rescue refers to its use "after high-dose methotrexate therapy in osteosarcoma," which is an approved indication for methotrexate.[201] Similarly, methotrexate's labeling refers to an approved use of Leucovorin Rescue.[202]

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[198] A recent article noted: "To obtain FDA approval for an additional use of a previously approved drug, the sponsor must submit a supplemental application (sNDA, sBLA, or sPMA) demonstrating the safety and efficacy of the drug when used in the new way or for the new indication. The supplemental application typically requires clinical data similar to those in the original application, but does not require the same extensive chemistry, manufacturing and controls, and preclinical pharmacology and toxicology data as in the original application." Shane M. Ward, "*Washington Legal Foundation* and the Two-Click Rule: The First Amendment Inequity of the Food and Drug Administration's Regulation of Off-Label Drug Use Information on the Internet," *Food and Drug Law Journal* 56 (2001): 41-56, at 44 (citations omitted).

[199] *See* 21 C.F.R. § 314.70(b). *See also* Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Univ. of Virginia Law Review* 82 (1996): 1753-1866, at 1775 ("FDA takes the position, which no manufacturer has sought to challenge in court, that any potentially significant modification of an approved new drug [application] likewise requires advance agency approval. As a consequence, not only attempts to expand the indications for a drug but other changes in labeling, in inactive ingredients, in the method or location of manufacture, or in packaging must first be the subject of an approved Supplemental New Drug Application.").

[200] *See* 21 C.F.R. § 201.57(c)(1)(iv).

By contrast, in the Mifeprex labeling, an *unapproved* indication for misoprostol is discussed. In approving such labeling, FDA has taken the aberrant position that the maker of one drug (Mifeprex) can secure approval of a new indication for another company's drug (misoprostol) merely by describing that new use as part of a combined therapy. FDA circumvented its own regulations by failing to require that both drugs in the Mifeprex Regimen be approved for the indication in question – pregnancy termination.[203]

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[201] *See* Leucovorin Calcium for Injection Package Insert ("Indications and Usage") ("Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists."). The package insert is available at: <http://www.xanodyne.com/leucovorin_calcium_pl_2002.pdf>.

[202] The methotrexate package insert states that "[m]ethotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor." The package insert is available at: <http://www.rxlist.com/cgi/generic/mtx_ids.htm>.

[203] A recent approval of a biologic product also illustrates the principle that FDA-approved labeling lists only approved indications. On February 19, 2002, FDA approved Zevalin for use in combination with Rituxan (rituximab) to treat low-grade B-cell non-Hodgkins Lymphoma (NHL). Rituxan had been approved previously and was already indicated "for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma." *See* Rituxan Package Insert ("Indications and Usage"). Rituxan and Zevalin are monoclonal antibodies that can significantly shrink tumors by targeting white blood cells (B-cells) including malignant B cells. The "Indications and Usage" section of Zevalin's label describes the drug as being "part of the ZEVALIN therapeutic regimen (see Dosage and Administration)." The "Dosage" section directs that Rituxan be administered and then followed by Zevalin on Day One and then again seven to nine days later. After the Zevalin NDA was approved, detailed information about the administration of the "Zevalin Therapeutic Regimen" was added to the Rituxan label. On February 19, 2002, FDA's Center for Biologics Evaluation and Research approved a supplement to the Rituximab biologics license application "to revise the dosage and administration section of the package insert to include information regarding the use of Rituximab as a component of the Zevalin therapeutic regimen . . . ." Letter, Dr. Karen D. Weiss, M.D., Director, Division of Clinical Trial Design and Analysis, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, to Alice Wei, IDEC Pharmaceuticals (Feb. 19, 2002) (*see* <http://www.fda.gov/cber/approvltr/rituide021902L.htm>).

2. FDA Sanctioned the Promotion of Misoprostol for an Unapproved Use as Part of the Mifeprex Regimen

The use of misoprostol as an abortifacient is an unapproved or "off-label" use.[204] FDA objects to the *promotion* of off-label uses of drugs by manufacturers.[205] "Off-label" uses of drugs are common as physicians explore new ways of using approved drugs, but normally FDA strives to ensure that physicians and patients are not misled into believing that FDA has approved such uses. In an effort to curb the promotion of off-label uses by pharmaceutical manufacturers, FDA issued regulatory guidance in 1996 pertaining to the dissemination of off-label use information.[206] In this case, however, FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol. FDA oversaw the creation of the promotional materials for Mifeprex,[207] which discussed the off-label use of misoprostol.[208] FDA itself disseminated information about

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[204] *See generally* James M. Beck and Elizabeth D. Azari, "FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions," *Food & Drug Law Journal* 53 (1998): 71-104, at 71 n.2, which explains "off-label" use as follows:

> "Off-label" has more accurately been termed "extra label" use. It means only that a product is used for a condition or in a way not appearing on its FDA-regulated labeling, not that the agency has judged the use adversely. *See, e.g., Washington Legal Found. v. Kessler*, 880 F.Supp. 26, 28 n.1 (D.D.C. 1995). . . . Off-label can mean many things. "[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use." William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993) (footnotes omitted).

[205] *See, e.g., Subpart H Final Rule*, 57 Fed. Reg. at 58,953 ("Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and that FDA has approved.").

[206] *See* FDA, "Advertising and Promotion; Guidances," Notice, 61 Fed. Reg. 52,800 (Oct. 8, 1996) (publishing two guidance documents: "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data" and "Guidance for Industry Funded Dissemination of Reference Texts").

[207] FDA reminded the Population Council in the Mifeprex Approval Letter that, pursuant to 21 C.F.R. § 314.550, the drug sponsor is obligated to submit Mifeprex promotional material for review by the agency prior to dissemination to physicians and the public. *See* Mifeprex Approval Letter at 3.

[208] A Danco Laboratories webpage, for example, contains the following question and answer:

> Q: How Does Mifeprex Work?
>
> A: Mifeprex blocks progesterone, a hormone necessary for a pregnancy to continue. You take Mifeprex followed by a prostaglandin, misoprostol, which causes uterine contractions that help to end pregnancy.
> In more detail, Mifeprex blocks progesterone, a naturally produced hormone that prepares the lining of the uterus for a fertilized egg and helps maintain pregnancy. Without progesterone, the lining of the uterus

the off-label use of misoprostol in documents such as the press release announcing the approval of Mifeprex for use in conjunction with misoprostol.[209] Recently it did so again when the agency emphasized the importance of adhering to the approved regimen, including the off-label use of misoprostol.[210]

3. Mifeprex Is Misbranded: Its Labeling Promotes an Unapproved Use of Another Drug

The labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved.[211] FDA's ability to regulate the marketing and distribution of drugs rests largely on its legal capacity to strictly control the content of a drug's labeling. A fundamental tenet of drug regulation is that FDA requires approval for every indication listed in the labeling of a drug.[212] FDA would undercut its own authority if it did not also apply this rule to uses for a drug referenced on another drug's labeling.

The Mifeprex labeling creates false expectations about misoprostol. Physicians and patients are justified in believing that any use or indication for a drug, included in the "Indication

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> softens, breaks down and bleeding begins. Mifeprex is followed by a prostaglandin that causes the uterus to contract, which helps to complete the process. . . . The prostaglandin used following Mifeprex is misoprostol, a drug already available in the United States.

"Using Mifeprex: Frequently Asked User Questions," Danco Laboratories website at <http://www.earlyoptionpill.com/may_faqs.php3>. The electronic version of the Mifeprex Label contains a hyperlink to the Danco Laboratories website, <www.earlyoptionpill.com>, which contains the above-referenced webpage. (When printed, the hyperlink appears to be ordinary text.)

[209] *See*, FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000) ("Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin.").

[210] *See* FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 6. In this same document, however, FDA cautions health care providers against "using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses . . . ." *Id.* at Question 9.

[211] Misoprostol receives more than a passing mention on the Mifeprex Label; the word "misoprostol" appears 34 times (compared to 57 appearances of "mifepristone" and 34 appearances of "Mifeprex").

and Usage" section of an FDA-approved label, has been subjected to the rigorous approval process set forth in Section 505 of the FD&C Act. Section 201.6(a) of the Agency's rules states that misbranding may arise from "a false or misleading representation with respect to another drug."[213] "When a physician, manufacturer, or *other third party* steps in to promote an unapproved use of a drug by advertising or distribution to other physicians, the drug may become unlawful under Section 301(k) the FD&C Act, 21 U.S.C. § 331(k)(1994), which prohibits misbranding, and Section 502(f)(1), 21 U.S.C. § 352(f)(1)(1994), which requires a drug's labeling to bear 'adequate directions for use.'"[214] Mifeprex is, therefore, misbranded.

Mifeprex is also misbranded because it is unsafe when used as directed in the approved labeling. Section 502(j) of the FD& C Act states that "[a] drug or device shall be deemed to be misbranded . . . [i]f it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof."[215] As discussed in the next section, FDA's approved regimen is unsafe because it lacks important safeguards.

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[212] *See* Elizabeth A. Weeks, "Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use under the Food and Drug Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 645-65, at 647 n.13 (citing Merrill, (*infra* Appendix A), at 1853).

[213] *See* 21 C.F.R. § 201.6(a).

[214] Merrill, *infra* Appendix A, at n.318 (emphasis added). *See also* 21 C.F.R. § 314.530(a)(5) (authorizing the Secretary to withdraw approval of a Subpart H drug if "[t]he promotional materials are false or misleading").

[215] 21 U.S.C. § 352(j). *See also* Jeffrey N. Gibbs and Judith E. Beach, "Chapter 7: Adulteration and Misbranding of Drugs" in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 229 ("When the drug is dangerous to the health of the user even when used as recommended on the label, it is misbranded.").

G. WOMEN'S LIVES ARE BEING ENDANGERED BY THE LACK OF SAFEGUARDS IN FDA'S APPROVED REGIMEN

On February 18, 2000, FDA informed the Population Council that "adequate information ha[d] *not* been presented to demonstrate that [mifepristone], when marketed in accordance with the terms of distribution proposed [by the Population Council], is safe and effective for use as recommended."[216] Over the next several months, the Population Council and Danco refused to supplement its distribution plan with a meaningful patient safety component. This prompted FDA, on June 1, 2000, to privately convey to the sponsor a set of proposed restrictions intended to rectify the sponsor's omission. The agency's proposed restrictions were soon leaked to the public. Amidst a vigorous political and editorial backlash, the sponsor not only rejected FDA's proposal but, in what was described by FDA as a "very significant change," repudiated restrictions the sponsor itself had proposed in 1996.[217] FDA succumbed and soon approved a regimen that did not embody restrictions sufficient to address the agency's legitimate safety concerns.

Early in the approval process, FDA expressed its intention to place restrictions on the use of mifepristone.[218] FDA's position was informed, in part, by the international experience with mifepristone.[219] The NDA submitted by the Population Council on March 14, 1996 included a plan that would have limited distribution of mifepristone to "licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and [redacted]), who will attend educational seminars on the safe use of this regimen."[220]

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[216] 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5 (emphasis added).

[217] *See* FDA Email (June 23, 2000): at 1 (explaining that the Population Council's attorney "affirmed that the 1996 proposals for distribution system as presented by the Pop Council then and agreed to by the [FDA Advisory Committee] and FDA are NOT what the Pop Council wants today. I explained that this change is very significant and that they need to provide their justification/rationale.")[FDA FOIA Release: MIF 002523].

[218] In order to allay concerns of the drug's European owner, FDA pledged, in the course of securing the U.S. patent rights for the Population Council, to "take appropriate measures . . . to assist through the NDA-approval process in the creation of a regime for the distribution and use that will protect against misuse of the drug." Letter, David A. Kessler, Commissioner of Food and Drugs, to the President & CEO of Roussel Uclaf [name redacted] and to Margaret Catley-Carlson, President of Population Council (May 16, 1994): at 1 [FDA FOIA Release: MIF 004992-93].

The FDA Advisory Committee, when it met in July 1996, was not satisfied with the restrictions proposed by the Population Council and expressed "serious reservations on how [the proposed drug distribution system] is currently described in terms of assuring safe and adequate credentialing of providers."[221] The Committee recommended additional restrictions designed to ensure "that this drug not be expanded to hands of physicians who are not already skilled in managing pregnancies, terminations, and complications of both."[222] Accordingly, FDA's 1996 Approvable Letter required the submission of "a comprehensive description of the proposed distribution system."[223]

In subsequent submissions, however, the Population Council insisted that the drug was safe and proffered restrictions designed primarily to control the manufacturing and retailing of the drug product. On August 18, 1999, the Population Council proposed to:[224] (i) limit the number and type of distributors; (ii) limit distribution to distributor-registered physicians who had provided certain assurances;[225] and, (iii) make available "training materials and information" and medical consultation to health care providers and product information to patients.[226] On January 21, 2000, Danco opined that "[r]egardless of the distribution system for mifepristone, the medical safety of this drug is well documented."[227] and proposed a distribution system that was designed only to ensure that Danco would "exert[ ] positive control over distribution of Mifeprex® through all phases of manufacturing, storage, shipment and administration from manufacturer to patient."[228]

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[219] In Europe, for example, mifepristone is used under more highly controlled conditions than were ultimately required in the United States. *See* Amendment to NDA 20-687, International Product Labeling with English Translations (submitted March 21, 2000) (presenting English translation of mifepristone product label, approved July 6, 1999, used in Austria, Belgium, Denmark, France, Germany, Greece, the Netherlands and Spain)[FDA FOIA Release: MIF 000493-506].

[220] Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62].

[221] FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45].

[222] FDA Memorandum, "Highlights of the July 19, 1996 Reproductive Health Products Advisory Committee (AC) Meeting on Mifepristone: Outstanding Issues for FDA to Address" (undated): at 3-4 [FDA FOIA Release: MIF 000534-38].

[223] 1996 Mifepristone Approvable Letter , *infra* Appendix A, at 1.

In reaction to the sponsor's recalcitrance, FDA took the position "that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[229] The agency nevertheless continued to encourage the sponsor to take an active role in devising appropriate restrictions on the use of mifepristone. Instead, in March 2000, the Population Council again protested that such restrictions were unwarranted.[230] It submitted a

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[224] *See* Medical Officer's Review, *infra* Appendix A, at 21-23 (setting forth the Population Council's complete response submitted to FDA on August 18, 1999).

[225] The physician would be required to provide a *self*-attestation covering the physician's ability to accurately date pregnancies and determine the patient's blood Rh factor and the physician's access to emergency medical facilities. Registering physicians would also agree to obtain from each patient an acknowledgement that she has received full information and is willing to comply with the treatment regimen, to maintain certain records (including ultrasound and blood test records) for each patient, to report adverse events and information about ongoing pregnancies, and to "[u]se every effort to ensure patients return for their follow up visit 14-20 days after taking the product." *See* Medical Officer's Review, *infra* Appendix A, at 22-23.

[226] *See* Medical Officer's Review, *infra* Appendix A, at 23.

[227] Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26]. Danco attempted to attribute any deleterious effects of mifepristone abortions to misoprostol: "More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin." *Id.* at 2.

[228] *See* Amendment 039 to the NDA, Mifeprex Distribution Plan Executive Summary (Jan. 21, 2000): at 3 [FDA FOIA Release: MIF 000530-31].

[229] *See* 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5. *See supra* Section III.C.2 and III.D. for a discussion of Subpart H, Section 314.520, which is reserved for drugs that are so inherently dangerous that their distribution and use must be restricted.

[230] In the course of objecting to the approval of the drug under subpart H, which is "likely to falsely 'mark' mifepristone as a highly toxic and risky drug," the Population Council insisted that "the FDA knows, [Mifeprex] is

distribution plan that it characterized as "detailed and comprehensive" and "surely equal to its purpose."[231] Once again, the plan consisted of restrictions intended only to control the manufacturing and retailing of the drug product.[232] Again FDA objected that "[t]he proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient."[233] The agency requested "that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product."[234]

On June 1, 2000, FDA proposed the following set of "Qualifications for Physician Recipients:" (1) the physician must demonstrate that she is licensed to practice medicine; (2) the physician must be "trained and authorized by law" to perform surgical abortions; (3) the physician must have "been trained to and ha[ve] the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination;" (4) the physician must have "satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications;" and

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exceptionally safe and effective." Responses by Population Council to "FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)" (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24]("March 2000 Response").

[231] March 2000 Response, *infra* Appendix A, at 2.

[232] Specifically, the plan provided for "secure manufacturing and shipping procedures, controlled returns, tracking of distribution of individual packages to the patient level, use of a limited number of distributors [redacted], account registration and other detailed ordering requirements for practitioners, direct distribution only to practitioners (not through retail pharmacies), and the use of signed patient agreements." March 2000 Response, *infra* Appendix A, at 2.

[233] Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1 [FDA FOIA Release: MIF 007811-13].

[234] Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1. FDA wanted the sponsor to provide a set of auditable provider qualifications, a plan for auditing providers to ensure that they were meeting these criteria, and an arrangement for discontinuing distribution to unqualified providers. *See id.* at 2.

(5) the physician must have "continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour's] drive from the treatment facility."[235] FDA's proposals were intended to address concerns about the safety of the women undergoing mifepristone-misoprostol abortions that the Population Council and Danco had refused to take into account in crafting restrictions for the drug.[236]

The Population Council and Danco objected strenuously to the proposed restrictions and aired their complaints in public.[237] FDA reprimanded the Population Council for leaking the restrictions to the public and misrepresenting the nature of the restrictions.[238] The Executive Vice President of the American College of Obstetricians and Gynecologists submitted an analysis of the leaked restrictions to FDA.[239] The editorial and political reaction,[240] together with the impending approval deadline of September 30, 2000,[241] however, had the desired effect of undermining FDA's resolve.

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[235] *See* FDA, "FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00" (June 1, 2000)[FDA FOIA Release: MIF 000522]. *See also* American College of Obstetricians and Gynecologists, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000): at 1 (setting forth FDA's second proposed restriction, which is redacted in the publicly available copy of FDA's proposal; also providing the redacted portion of the fifth restriction)[FDA FOIA Release: MIF 001366-69].

[236] It should be noted, that even these restrictions would not have been sufficient to make mifepristone-misoprostol abortions safe. Among the key safeguards missing from FDA's proposal were requirements that every prospective patient undergo an ultrasound and that prescribing physicians be required to have admitting privileges at facilities able to provide emergency care.

[237] Paul Blumenthal, M.D., Jane Johnson, and Felicia Stewart, M.D., "The Approval of Mifepristone (RU486) in the United States: What's Wrong with this Picture?" *Medscape Women's Health* 5 (2000) (reproduced in an internal FDA email)[FDA FOIA Release: MIF 00002597-99] ("At a meeting of early abortion providers and abortion advocates, the Population Council and Danco revealed that the U.S. Food and Drug Administration (FDA) had made a series of proposals regarding the labeling and distribution of mifepristone that would severely limit women's access to the drug if and when it is approved.").

[238] *See* Teleconference Meeting Minutes (between FDA staff and representatives of the Population Council and Danco) (June 7, 2000): at 1 ("Meeting Objective: . . . to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.")[FDA FOIA Release: MIF 002136-37]; FDA internal email (June 23, 2000): at 1 (re: telephone conversation with Population Council attorney, Nancy Buc, on 6/23/00) ("I also said that we were looking to Pop Council to be a responsible entity in manufacturing, distributing, and shepherding this drug and that most responsible entities make proposals rather than expect FDA to write labels and distribution systems and obtain comments through the media.")[FDA FOIA Release: MIF 002523].

[239] *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) to Jane Henney, M.D. (July 24, 2000) and enclosure: ACOG, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000)[FDA FOIA Release: MIF 001366-69]. ACOG and the American Medical Association ("AMA") also attempted to secure a meeting with

At a meeting on July 19, 2000, FDA yielded to the Population Council and Danco on a number of important issues.[242] FDA abandoned its proposal for auditable physician qualifications and agreed instead to permit physicians to attest to their own qualifications.[243] Instead of requiring formal training, FDA merely "request[ed] that the physician also attest to having read and understood the training materials and labeling."[244] FDA also agreed not to

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Dr. Jane Henney, FDA Commissioner, and her staff, in order to further discuss their opinion of the restrictions. *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) and E. Ratcliffe Anderson, Jr., M.D. (Executive Vice President, AMA) to Jane Henney, M.D. (July 24, 2000): at 1 ("The undersigned organizations . . . are very concerned about restrictions . . . [FDA] has proposed for . . . mifepristone We would like the opportunity to meet with you and your staff to discuss this important issue. It's imperative that the FDA fully understands the effect that these proposals would have on the quality of health care. It's equally imperative that the FDA's work be based solely on evidence from the drug's clinical trials, and be entirely from political influence.")[FDA FOIA Release: MIF 001363]. They were permitted only to meet with officials in FDA's Office of Women's Health, an office within the agency that was not involved in reviewing the NDA. *See* Letter, Jane Henney to Hale and Anderson (Aug. 11, 2000): at 1-2 [FDA FOIA Release: MIF 001361]. The questionable scientific basis for this challenge to FDA's proposed restrictions was recently brought to the attention of ACOG by one of the Petitioners. Letter, Donna Harrison, M.D. (Chairperson, AAPLOG Committee on Mifeprex Use) to Ralph Hale, M.D. (Executive Vice President, ACOG) (May 23, 2002) (available at <http://www.aaplog.org/acogmifeprexletter.htm>).

[240] *See, e.g*, Letter, U.S. Senator Barbara Boxer to Dr. Jane Henney (June 9, 2000): at 1 ("According to news reports, the FDA is considering placing draconian restrictions on the accessibility of RU-486 as a condition of its approval . . . . In 1996, the FDA found RU-486 to be safe and effective. Therefore, it is a mystery to me why the FDA would even consider restricting access to it.")[FDA FOIA Release: MIF 006376]; Letter, Mark Green, Public Advocate for the City of New York, to Dr. Jane Henney (Sep. 22, 2000): at 1 ("Earlier this week Planned Parenthood of New York City, NARAL-New York, the Access Project and Physicians for Reproductive Health and Choice joined me in convening a public hearing in New York City on pending action by [FDA] on mifepristone . . . . [I am] also concerned about the restrictions on access to RU-486 that FDA is said to be considering.")[FDA FOIA Release: MIF 001288-1302]; Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times* (June 8, 2000): at A21 ("The long-running effort to bring the French abortion pill to women in this country has encountered yet another obstacle: a suggestion by [FDA] that it may place tight restrictions on how the drug, RU-486, is distributed and who can prescribe it."); Letter, U.S. Representative Lynn Woolsey to Dr. Jane Henney (June 22, 2000): at 1 ("However, I am deeply concerned about recent press reports about proposed restrictions.") [FDA FOIA Release: MIF 006372].

[241] As noted above, because FDA had accorded priority review to mifepristone, the approval process was slated for completion by September 30, 2000.

[242] *See* Meeting Minutes, re: Approvability Issues Related to Labeling and Distribution Plan for Mifepristone (July 19, 2000): at 2-4 [FDA FOIA Release: MIF 004661-65].

[243] *See id.* at 2.

[244] *Id.* at 2.

require pre-procedure ultrasounds.[245] Furthermore, FDA stated "that it is not necessary to require the patient to take the drugs in the presence of health care provider."[246]

Among the unresolved issues at the conclusion of the July 19, 2000 meeting was the question of whether prescribing physicians should be limited to those who were able to perform surgical abortions, a provider qualification FDA believed was necessary:

> FDA requests that the ability to perform vacuum aspirations and/or D&Cs be added to provider qualifications. Providers also need to have access to emergency services. The need for surgical intervention is predictable unlike with other drugs. All OB/GYNs and other practitioners of women's health have these skills. The countries with experience with mifepristone have tight provision of complete services and have a long record of good outcomes.[247]

The Population Council later rejected FDA's request,[248] and the agency acquiesced.[249]

Despite its persistent concerns, FDA approved a regimen that posed the very risks to women's health that the agency had previously identified. When it approved Mifeprex, FDA stated that "[u]nder 21 CFR 314.520, distribution of the drug is restricted as follows:"

> Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:
>
> - Ability to assess the duration of pregnancy accurately.
> - Ability to diagnose ectopic pregnancies.
> - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
> - Has read and understood the prescribing information of Mifeprex™.

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[245] *See id.* at 3.

[246] *Id.* at 3.

[247] *Id.* at 3.

[248] *See* Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 6 (arguing that bolstering the provider qualifications in this way would be "not only unnecessary, but also in fact potentially counterproductive for patients")[FDA FOIA Release: MIF 0001373-81].

[249] *See* Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 [FDA FOIA Release: MIF 004587-88].

- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement, and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's records.[250]

In addition, the restrictions include a requirement that distribution be carried out in accordance with the plan submitted to FDA by the Population Council in a March 30, 2000 submission.[251] Even as it assented to a regimen that lacked critical safeguards, FDA took a number of steps that indicated its lingering concerns about the safety of the drug. First, FDA ultimately decided to rely on an infrequently used provision in Subpart H in hopes of ensuring that mifepristone would be used safely and, if necessary, could be withdrawn from market rapidly.[252] Second, the staff insisted that the mifepristone label "include a black boxed warning describing the major requirements and conditions for use."[253] "FDA generally reserves boxed warnings for serious or life-threatening risks that best can be minimized by conveying critical information to the prescribing doctor in a highlighted manner."[254]

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[250] Mifeprex Approval Letter at 2.

[251] *See* Mifeprex Approval Letter at 2.

[252] *See* 21 C.F.R. 530 ("Withdrawal Procedures"). *See also* FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85]. As late as July 19, 2000, the question of whether to use Subpart H was deemed to be an "Outstanding Issue." *See* Meeting Minutes, re: Approvability Issues (July 19, 2000): at 4 [FDA FOIA Release: MIF 004661-65].

[253] FDA, Memorandum, re NDA 20-687 (Feb. 17, 2000): at 2. The Population Council, which opposed the inclusion of such a warning, ultimately persuaded FDA to agreed to a pared-down Black Box Warning, which would merely direct the prescribing physician (i) to plan in advance for emergency care, and (ii) to make available to the patient and provide her with the opportunity to discuss the patient information and patient agreement. *See* Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 1-2 [FDA FOIA Release MIF 0001373-81].

FDA's willingness to tailor the restrictions on Mifeprex to suit the demands of the Population Council and Danco will continue to manifest itself in serious adverse events among the women who use the Mifeprex Regimen. Some of the most critical flaws in the approved regimen are discussed below along with serious adverse events that have already been reported.

1. The Approved Regimen Is Unsafe Because It Does Not Require Ultrasound

a. Ultrasound Is Necessary to Accurately Date Pregnancies

The gestational age of a woman's pregnancy is a critical factor in determining whether she is an appropriate candidate for a mifepristone abortion. In order to minimize the risks of hemorrhage, incomplete abortion and continuing pregnancy, the gestational age of the pregnancy must be less than or equal to 49 days.[255] The authors of the Spitz Article, for example, found that "[f]ailures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of the pregnancy."[256] Through the combination of mifepristone and misoprostol, "pregnancy was terminated in 762 of the 827 women pregnant for [less than or equal to] 49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) . . . ."[257] The study also found that "[a]bdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age."[258] Due to the significant increase in failures and complications with increasing gestational age, FDA approved Mifeprex only for pregnancies of less than or equal to 49 days' gestation.[259]

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[254] Judith E. Beach et al., "Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs," *Food and Drug Law Journal* 53 (1998): 403-412, at 403 (available at: <http://www.fdli.org/pubs/Journal%20Online/53_3/art2.pdf>). *See also* 21 C.F.R. § 201.57(e) ("Warnings").

[255] As noted above, the gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy.

[256] Spitz Article, *infra* Appendix A, at 1241. "The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the [less than or equal to] 49-days group to 9 percent in the 57-to-63 days group (P<0.001)." Children born from ongoing pregnancies, after a failed application of the Mifeprex Regimen, may suffer birth defects, fertility problems, or other health problems later in life. Researchers have found evidence linking misoprostol and birth defects such as missing or deformed limbs and misshapen skulls. Much of this research was conducted in Brazil, where numerous women have attempted to induce abortions using misoprostol alone. *See, e.g.,* Sylvia Pagán Westphal, "Birth Defects Caused by Ulcer Drug Abortions," *NewScientist.com* (29 Aug. 2001) ("Several studies in Brazil, where up to 75 percent of clandestine abortions involve misoprostol, suggest the drug causes birth defects such as fused joints, growth retardation and a condition known as Möbius syndrome, which is characterised by paralysis of the face."); Iêda M. Orioli and Eduardo E. Castilla, "Epidemiological

The only way to date a pregnancy with the degree of accuracy necessary to exclude women whose pregnancies are beyond 49 days' gestation is by use of transvaginal ultrasound. FDA severely undermined the limitation on gestational age, however, when it failed to require

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Assessment of Misoprostol Tetratogenicity," *British Journal of Obstetrics and Gynaecology* 107 (April 2000): 519-23, at 522 (". . . there is an association of prenatal use of misoprostol as an abortifacient and congenital defects of vascular disruption type."); F.R. Vargas *et al.*, "Prenatal Exposure to Misoprostol and Vascular Disruption Defects: A Case-Control Study," *American Journal of Medical Genetics* 95 (2000): 302-306, at 306 ("add[ing] epidemiological basis to the growing body of evidence that prenatal exposure to misoprostol is related to the occurrence of vascular disruption defects in some exposed fetuses."). FDA determined that data submitted by the Population Council from a survey of fetal abnormalities in 82 pregnancies that were exposed to mifepristone alone or in combination with misoprostol was inconclusive. *See* FDA Mifeprex Approval Memorandum, *infra* Appendix A, at 4. FDA acknowledged, however, the possible link between misoprostol and birth defects. *See* Medical Officer's Review, *infra* Appendix A, at 18 (". . . medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)."). The need for a study of the possible joint effects of mifepristone and misoprostol on babies born after a failed application of the Mifeprex Regimen was highlighted by the abnormalities discovered in a fetus exposed to misoprostol and mifepristone. *See* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Number 3877547-X (March. 1, 2002) (French report of numerous deformities in fetus that was exposed to mifepristone and misoprostol but survived until a subsequent surgical abortion was performed; "The anatomopathology examination showed a meningo-encephalocele. The left hand was constituted of only two fingers (oligodactylia), left and right foot were constituted of only one finger (monodactylia). There was a facial dysmorphia.").

[257] Spitz Article, *infra* Appendix A, at 1241.

[258] Spitz Article, *infra* Appendix A, at 1241. In order to treat vaginal bleeding, "[t]wo percent of the women in the [less than or equal to] 49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids (P=0.008)." *Id.*

[259] FDA's Medical Officer's Review noted: "The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age." Medical Officer's Review, *infra* Appendix A, at 18. The review stated further: "This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period." *Id.*

the ultrasound dating of pregnancies. FDA's approved regimen relies instead on a patient's recollection of her menstrual history and a physical examination. Dating based on menstrual history is inherently inaccurate because women may not have a perfect 28-day menstrual cycle[260] and because 25 percent of women experience bleeding during the early stages of pregnancy.[261] Gestational dating through physical examination, even when carried out by experienced clinicians, can also be inaccurate.[262] Factors such as patient body size, uterine fibroids, previous parity, and uterine position may impair a clinician's ability to assess uterine size.[263] Transvaginal ultrasound, by contrast, is accurate within plus or minus 3 days at gestational ages of 5 to 7 weeks.[264] "Transvaginal ultrasonographic examination is necessary to ensure accurate gestational dating for provision of medical abortion according to current standards in clinical guidelines established by the National Abortion Federation."[265]

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[260] *See, e.g.,* Leon Speroff, M.D., Robert H. Glass, M.D., and Nathan G. Kase, M.D., *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 219 ("The perfect 28 day cycle is indeed the most common mode, but it totaled only 12.4% of Vollman's cycles. Overall, approximately 15% of reproductive age cycles are 28 days in length. Only 0.5% of women experience a cycle less than 21 days long, and only 0.9% a cycle greater than 35 days. Most women have cycles that last from 24-35 days, but at least 20% of women experience irregular cycles.").

[261] *See* Peter W. Callen, M.D., *Ultrasonography in Obstetrics and Gynecology* 2nd ed. (Phila, Pa: W.B.Saunders Company; Harcourt, Brace, Jovanovich, 1988) at 32 ("Threatened abortion is a common complication that occurs in approximately 25% of clinically apparent pregnancies."); Speroff, *et al*, *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 536 (noting that "pregnancy and pregnancy-related problems such as ectopic pregnancy or spontaneous abortion" can cause uterine bleeding).

[262] Steven R. Goldstein, M.D., Francis R. M. Jacot, M.D., Claude Poulin, M.D., and D. Scott Poehlmann, M.D., "Documenting Pregnancy and Gestational Age," Chapter 4, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999) ("*A Clinician's Guide*"): at 41 ("Although clinical sizing of the uterus during the first trimester can provide a rough estimate of gestational age, it is imprecise; misestimation of gestational age by uterine sizing alone can occur even in the hands of experienced clinicians.").

[263] *See A Clinician's Guide, infra* Appendix A, at 41 ("a number of conditions such as leiomymas, multiple gestation, and obesity may severely limit the accuracy of gestational age assessment by physical examination, warranting preprocedure assessment by ultrasonography in known or suspected cases") (footnotes omitted).

[264] *See* Salim Daya, M.B., "Accuracy of Gestational Age Estimation Using Fetal Crown-rump Measurements," *American Journal of Obstetrics and Gynecology* 168 (March 1993): 903–908; Ivar K. Rossavik, M.D., George O. Torjusen, M.D., and William E. Gibbons, M.D., "Conceptual Age and Ultrasound Measurements of Gestation Age and Crow-Rump Length in *in Vitro* Fertilization Pregnancies," *Fertility and Sterility* 49 (1988): 1012-17. *See also* Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and.Gynecology* 180 (1999): 35-41. In this study comparisons of gestational age estimates based on the last reported menstrual period to those generated through ultrasound in patients presenting for medical abortion, revealed the former method to be significantly inaccurate in approximately half the cases. The authors observed: "It is interesting that in this population of women seeking abortion the gestational age according to the LMP [last menstrual period] was verified

b. Ultrasound Is Necessary to Identify Ectopic Pregnancies

Approximately two percent of all pregnancies in the United States are "ectopic pregnancies," in which the pregnancy is located outside the uterus – often in the fallopian tube.[266] Mifeprex does not terminate ectopic pregnancies.[267] Therefore, if a woman who has an ectopic pregnancy undergoes a mifepristone-misoprostol abortion, she is at risk for tubal rupture and subsequent hemorrhage due to delay in diagnosis and delay in treatment. The symptoms of an ectopic pregnancy – vaginal bleeding, pelvic pain, and cramping – are confusingly similar to certain side effects of the Mifeprex Regimen.[268] A woman with an ectopic pregnancy is at risk of suffering massive intra-abdominal hemorrhage, damage to her reproductive organs, permanent

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by the transvaginal ultrasonographic examination only 48% to 56% of the time when a gestational sac was present and only 55% to 64% of the time when an embryonic pole was present . . . . These results, though, do not even include those women who were excluded from the studies because the ultrasonographic examination findings were so different from the dates by LMP that the estimation of gestational age was changed too much for them to be included." *Id.*

[265] Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and Gynecology* 180 (1999): at 35-41 (text preceding n. 8) (citation omitted).

[266] Centers for Disease Control, "Ectopic pregnancy – United States, 1990-1992," *Morbidity and Mortality Weekly Report* (*MMWR*) 44 (No. 3) (Jan. 27, 1995): at 46. The number of ectopic pregnancies may be even higher now because sexually transmitted diseases and other causes of ectopic pregnancy are more widespread than they were in 1992 – the latest year for which the Centers for Disease Control have reported the number of ectopic pregnancies. *Id.* at 46-7.

[267] *See, e.g.*, Beth Kruse *et al.*, "Management of Side Effects and Complications in Medical Abortion," *American Journal of Obstetrics and Gynecology* 183 (2000): S65-S75, at S72 ("Mifepristone has not proved effective in treating extrauterine pregnancy . . . .").

[268] *See* American College of Obstetricians and Gynecologists, "Medical Management of Abortion," *ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists* 26 (April 2001): at 6 (noting that in medical abortions, "women may even experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac or even an ectopic pregnancy") ("ACOG Practice Bulletin"). Vaginal bleeding, for example, is a normal consequence of the Mifeprex Regimen and may continue for weeks after a woman ingests Mifeprex and misoprostol. *See, e.g.*, Spitz, *infra* Appendix A, at 1243 ("Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated

sterility, and even death if not promptly treated by emergency surgery. The authors of a French mifepristone study in which a participant with an ectopic pregnancy underwent emergency surgery to stop heavy bleeding, concluded that:

> The case of undiagnosed ectopic pregnancy, which ruptured suddenly 2 days after misoprostol intake, indicates that (1) mifepristone plus misoprostol is not an effective treatment of ectopic pregnancies and should not be used for this purpose, and (2) all medical means of detecting an ectopic pregnancy should be used before prescribing mifepristone plus misoprostol.[269]

Although the Mifeprex Label states that the Mifeprex Regimen is contraindicated for women with a "[c]onfirmed or suspected ectopic pregnancy,"[270] FDA did not require that ultrasound be used to exclude women with ectopic pregnancies. Instead, the approved regimen relies solely on a self-certification by the prescribing physician that she has the "[a]bility to diagnose ectopic pregnancies."[271] A physical examination alone cannot accurately identify ectopic pregnancies. Ultrasound, "[i]n addition to providing the best information for gestational age determination . . . can also provide useful diagnostic information regarding a wide variety of pathologies of early pregnancy," including ectopic pregnancies.[272]

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medically. The median duration of bleeding or spotting was 13 days in the [less than or equal to] 49-days group and 15 days in the other two groups (P<0.001).").

[269] Elizabeth Aubény, *et al.*, "Termination of Early Pregnancy (Up to 63 Days of Amenorrhea) with Mifepristone and Increasing Doses of Misoprostol," *International Journal of Fertility & Menopausal Studies* 40 (1995): 85-91, at 91.

[270] *See* Mifeprex Label ("Contraindications").

[271] *See* Mifeprex Prescriber's Agreement.

[272] *A Clinician's Guide, infra* Appendix A, at 47-8.

2. FDA's Approved Regimen Is Not Restricted to Properly Trained Physicians who Have Admitting Privileges to Emergency Facilities

FDA's approved regimen lacks any objective qualifications for prescribing physicians and administering health care providers.[273] The health care provider administering the Mifeprex Regime need not undergo training, may not necessarily be an obstetrician or gynecologist, may not have any surgical training or training in the management of abortion complications, and may not even be a physician.[274] For example, the Mifeprex Regimen could be administered by a nurse untrained in any type of abortion and under the remote supervision of a family practitioner who does not regularly practice obstetrics and is incapable of providing emergency care.

Physicians and the health care staff that they supervise require formal training in both pharmaceutical and surgical abortion to minimize the morbidity inherent in performing mifepristone abortions.[275] National Abortion Federation guidelines provide that "[a]ll personnel performing abortions must receive training in the performance of abortions and in the prevention, recognition, and management of complications."[276] Additionally, ACOG recommends that "[c]linicians other than obstetrician-gynecologists who wish to provide medical abortion services should work in conjunction with an obstetrician-gynecologist or be trained in surgical abortion in order to offer medical abortion treatment."[277] The necessity for training in surgical abortion as well as mifepristone abortion stems primarily from the high failure rate of the Mifeprex Regimen. In the U.S. Clinical Trial, the Mifeprex Regimen failed for 8 percent of women with pregnancies of less than or equal to 49 days' gestational age.[278]

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[273] Self-certifications do not provide an effective substitute for imposing objective, auditable requirements. The Mifeprex Prescriber's Agreement, for example, merely requires that the prescribing physician profess to have the "[a]bility to assess the duration of pregnancy accurately." The vacuity of this stipulation is illustrated in remarks made by Dr. Susan Allen (who later became an FDA official) before the FDA Advisory Committee. Dr. Allen stated, "If you also recall when you go through medical school you learn how to date a pregnancy." FDA Hearings Transcript, *infra* Appendix A, at 319.

[274] *See* Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 ("the distribution system would allow for physicians to obtain the drug product after meeting all qualifications, but Mifeprex could be administered by someone who is under the supervision of that physician such as midwives or nurse practitioners")[FDA FOIA Release: MIF 004587-88]; *see also*, Mifeprex Approval Memo, *infra* Appendix A, at 4-5 ("Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician from dispensing the drug to patients, provided state laws permit this.").

[275] A survey of methotrexate abortion providers underscores the necessity of training in both medical and surgical abortion. *See* S. Marie Harvey, Linda J. Beckman, and Sarah J. Satre, "Experiences and Satisfaction with Providing Methotrexate-Induced Abortions among U.S. Providers," *Journal of the American Medical Women's Association* 55 (2000): 161-63, at 162 (In a study comparing methotrexate and surgical abortion, "[m]ost providers felt strongly that all clinic staff should be familiar with both procedures and, thus, the training needs would be equivalent. This thought was echoed not only by physicians, who must be prepared to perform an emergency surgical abortion if methotrexate fails, but also by other clinic personnel. Thirty-nine percent of providers thought that medical abortion

Excessive bleeding, which is much more common following a Mifeprex abortion than a surgical abortion, is particularly likely to necessitate urgent surgical intervention. Based on an international study comparing surgical and medical abortion, FDA's Medical Officer noted that "[o]n the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients" and characterized this as a "serious potential disadvantage of the medical method."[279] In the U.S. Clinical Trial among patients whose pregnancies were of no more than 49 days' gestation, excessive bleeding resulted in one blood transfusion, two hospitalizations, two emergency room treatments, and thirteen surgical interventions.[280] In

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required more training; specifically, learning to do a vaginal ultrasound and to handle the unpredictable outcomes of methotrexate abortion required lengthy training.").

[276] National Abortion Federation, "National Abortion Federation Clinical Policy Guidelines, 1998," Appendix, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999): at 256 ("*A Clinician's Guide*").

[277] ACOG Practice Bulletin, *infra* Appendix A, at 6.

[278] *See* Medical Officer's Review, *infra* Appendix A, at Table 1. Seventeen percent of women with pregnancies of between 50 and 56 days' gestational age and 23 percent of women with pregnancies between 56 and 63 days were failures. *See id.* In an international study reviewed by the Medical Officer, failure rates for mifepristone abortion were 5.2 percent, 8.6 percent and 16 percent in India, China and Cuba respectively, while comparable failure rates for surgical abortion were 0, 0.4 percent, and 4.0 percent. *See* Medical Officer's Review, *infra* Appendix A, at 19.

[279] Medical Officer's Review, *infra* Appendix A, at 19 (no citation by FDA Medical Officer).

[280] Medical Officer's Review, *infra* Appendix A, at 17.

addition, 5 percent of the patients in this group received uterotonic agents to stem bleeding.[281] A delay in intervention may be life-threatening,[282] as was illustrated by the experience of one of the participants in the U.S. Clinical Trial. The treating physician described the incident to the FDA Advisory Committee:

> In November of 1994, I was called to the [emergency room] for a woman who was bleeding due to a miscarriage, and was in obvious shock. A blood test showed that she had lost between one-half to two thirds of her blood volume . . . .
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> I had thought she was having an incomplete miscarriage, but her husband . . . told me that she had taken RU486 approximately 2 weeks before. It was my clinical opinion that she would die soon if she did not have an immediate [dilation and curettage].
>
> Without even doing the routine preparation we normally do for surgery, I realized that I had to take her immediately to surgery to save her life. I took her to the operating room and removed the contents of her uterus surgically. I gave her two units of packed red blood cells intraoperatively.
>
> Even later that evening, . . . [s]he required two more units of blood because she was still orthostatic and symptomatic.[283]

The Mifeprex Regimen is contraindicated for "any patient who does not have adequate access to medical facilities equipped to provide emergency treatment."[284] FDA's approved regimen, however, does not require prescribing physicians to have *admitting* privileges to emergency facilities. The approved regimen requires only that a physician who is not able "to provide surgical intervention in cases of incomplete abortion or severe bleeding . . . ma[k]e plans to provide such care through others, and [be] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[285] Plans for back-up care may be nothing more than "having the ability and responsibility to direct patients to hospitals, if needed."[286] Moreover, the approved regimen does not include an objective geographical limitation to ensure that the patient has easy access to the designated emergency care facility.[287]

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[281] Medical Officer's Review, *infra* Appendix A, at 17.

[282] When surgery is indicated because of acute bleeding, significant, or even life threatening blood loss, has already taken place. The preoperative preparation of the patient is often compromised in the rush to complete the surgery, which results in higher infection rates and more anesthetic complications, such as aspiration during intubation.

[283] FDA Hearings Transcript, *infra* Appendix A, at 223-25 (testimony of Dr. Mark Louviere).

[284] *See* Mifeprex Label ("Contraindications").

[285] Mifeprex Prescriber's Agreement. FDA, however, took two steps that suggested that it has lingering concerns about the absence of a surgical intervention qualification for Mifeprex prescribers. First, the Mifeprex Label includes a "black box" warning governing surgical back-up. Second, FDA required the Population Council to perform a post-approval study "[t]o ensure that the quality of care is not different for patients who are treated by

3. The Sponsor's Recent "Dear Doctor Letter" and FDA's Explanatory Webpage Announcing Serious Adverse Events Validate the Petitioners' Concerns

On April 17, 2002,[288] Danco, with FDA's assistance, issued a letter to health care providers to alert them to "New Safety Information," to remind them that Mifeprex was approved for use in a prescribed regimen, and to encourage them to provide patient counseling and report adverse events.[289] The "New Safety Information" consisted of a number of reports of serious adverse events that had been experienced by women who were undergoing or had

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physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention . . . ." Mifeprex Approval Memo, *infra* Appendix A, at 5.

[286] Mifeprex Approval Memo, *infra* Appendix A, at 5. FDA's decision not to include a requirement that the prescribing physician have admitting privileges at a hospital could delay the patient's admission for emergency care. Another likely consequence of not requiring the prescribing physician to have admitting privileges is underreporting of serious adverse events related to the Mifeprex Regimen. The treating physician, not privy to the Prescriber's Agreement, may not file a serious adverse event report or notify the abortion provider of the complications that arose from the Mifeprex Regimen.

[287] The Chinese experience with mifepristone suggests that mifepristone should not be administered in facilities unable to provide potentially necessary emergency services. Thus, recently, the Chinese State Drug Administration responded to concerns that women were suffering as a result of lax controls on mifepristone by reiterating its policy that the drug "can only be administered at a hospital under a doctor's supervision and cannot be sold at pharmacies even with a prescription." *See* Kaiser Family Foundation, "China Reaffirms Restrictions on Unsupervised Mifepristone Use," *Kaiser Daily Reproductive Health Report* (Oct. 15, 2001) (available at: <http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=2&DR_ID=7453>) (reporting also that, "[t]hree years ago, the Shanghai Health Bureau restricted the use of mifepristone to certain hospitals in the area because of fears of complications").

[288] The letter bears the date, April 19, 2002, but was disseminated to the public on April 17, 2002.

[289] Danco Laboratories, Open Letter to Health Care Providers (Apr. 19, 2002) ("Dear Doctor Letter") (available at: <http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf>). Coincidentally, on the same day FDA and Danco publicized these serious adverse events, the agency also announced major changes to the Cytotec (misoprostol) label. *See* FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). Pursuant to these labeling changes, pregnancy was removed from the list of contraindications on the Cytotec label and the black box warning cautioning pregnant women not to take the drug was also removed.

recently completed the Mifeprex Regimen.[290] A number of patients had suffered from ruptured ectopic pregnancies and one of these women died from hemorrhage.[291] The letter also reported "[t]wo cases of serious systemic bacterial infection (one fatal)."[292] The fatality apparently precipitated a halt in the Population Council's Canadian clinical trials of mifepristone.[293] Finally, a 21 year old woman suffered a heart attack three days after she completed the Mifeprex Regimen.[294] These and other adverse events had been reported to FDA through its Adverse Event Reporting System (AERS).[295] Two of the patients who were reported to have suffered life-threatening adverse events were 15 years old.[296] These incidents bear out the concerns about the safety of the regimen detailed above, and the relatively high rate of serious adverse events among adolescents is of particular concern.

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[290] The letter did not specify the number of adverse events about which Danco had been informed, but five individual cases were discussed.

[291] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[292] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[293] It appears that the woman reported to have died from a systemic bacterial infection was a Canadian trial subject. *See* Marnie Ko, "A Volunteer Dies While Testing a Controversial New Drug, Bringing the Trial to a Halt," The Report (Oct. 8, 2001) (available at: <http://report.ca/archive/report/20011008/p48ai011008f.html>). *See* also Henry P. Kaiser Family Foundation, "Population Council Announces Death of Woman Involved in Canadian Mifepristone/Misoprostol Trial," Daily Reproductive Health Report (Sept. 11, 2001) (available at: <http://www.kaisernetwork.org/Daily_reports/rep_index.cfm?DR_ID=6877>). A *Clostridium sordellii* infection apparently caused the woman to suffer septic shock. *See generally* G.L. Mandell, J.E. Bennett, and R. Dolin, *Principles and Practice of Infectious Diseases* (5th ed. 2000): at 2551 (explaining that a disease process in which "clostridia clearly play a major pathogenic role i[s] uterine gas gangrene, now a rare complication that was previously seen in the setting of septic abortion." "*C. sordellii* has been reported as a cause of uterine gas gangrene . . . ."). *See also* FDA Q & A's, *infra* Appendix A, at Question 3 ("Serious systemic bacterial infection is a severe life-threatening infection that spreads throughout the body and can cause death.").

[294] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[295] *See, e.g.*, Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3819498-2 (Nov. 2, 2001) (intervention to prevent permanent impairment or damage); 3806144-7 (Oct. 9, 2001) (death of a patient with an ectopic pregnancy); 3769840-6 (July 30, 2001) (hospitalization of patient with an ectopic pregnancy); 3769842-X (July 30, 2001) (intervention to prevent permanent impairment or damage); 3719885-7 (May 8, 2001) (death in conjunction with the use of misoprostol and Mifegyne, which is the trade name of mifepristone distributed in France); 3713452-7 (Apr. 27, 2001) (intervention to prevent permanent impairment or damage); and, 3769838-8 (July 30, 2001) (intervention to prevent permanent impairment or damage). The AERS depends on voluntary reporting and the accuracy of these reported adverse events cannot be verified, nor can the cause of these events be identified with certainty. There may have been other adverse events that were not reported.

Simultaneously with Danco's distribution of the *Dear Doctor Letter*, FDA published a webpage with 14 questions and answers related to mifepristone in an attempt to answer some of the questions likely to be prompted by the letter and to urge health care providers to adhere to the approved regimen.[297] FDA's answers, however, leave much to be desired from a medical and scientific standpoint.

First, FDA has understated the possibility that the Mifeprex Regimen caused the serious adverse events reported in the letter.[298] FDA did not adequately explain why women who were apparently healthy prior to undergoing the Mifeprex Regimen experienced life-threatening or fatal complications such as ruptured ectopic pregnancies, heart attacks, and systemic bacterial infections.

Second, FDA inappropriately attempted to link these adverse events to the unapproved vaginal administration of misoprostol.[299] It was reckless for FDA to suggest that the vaginal administration of misoprostol caused these adverse events while overlooking critical flaws in the

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[296] *See* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3803789-5 (Oct. 3, 2001) and 3815629-9 (Oct. 26, 2001).

[297] FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") (available at: <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm).

[298] *See* Dear Doctor Letter, *infra* Appendix A, at 1 ("No causal relationship between any of these events and use of Mifeprex and misoprostol has been established."). An FDA official interviewed (without attribution) downplayed the connection between the Mifeprex Regimen and the adverse events. *See* Susan Okie, "Physicians Sent Abortion Pill Alert: Six Women Using RU-486 Taken Ill, and Two Died, Letter Says," *Washington Post* (Apr. 18, 2002): at A2 ("These are, in fact, a very small number of events. Some of them were clearly not caused by the drug regimen.").

[299] The repeated references to the unapproved vaginal use of misoprostol in the FDA Q & As give rise to the inference that the reported adverse events are attributable to this single departure from the Mifeprex Regimen. *See, e.g.*, FDA Q & As, *infra* Appendix A, at Question 1 ("In all of these cases, misoprostol was given vaginally, not orally, which is the approved regimen. FDA has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol."); *id.* at Question 4 ("We do not know what role, if any, Mifeprex and 'off-label' use of vaginal misoprostol may have in developing serious infections."); *id* at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses? There are published studies of the use of mifepristone with vaginal administration of misoprostol for abortion. The misoprostol doses used in these studies are higher than those described in the Mifeprex labeling . . . ."); *id.* at Question 10 ("Are there risks with vaginal use of misoprostol?").

approved regimen for Mifeprex use in the United States. FDA should have first assessed essential aspects of this regimen.

It is clear, for example, that absent ultrasonographic screening for ectopic pregnancy, there is increased risk that an intact or rupturing ectopic pregnancy will be misdiagnosed as a normally progressing Mifeprex abortion. Additionally, Mifeprex abortions may be performed by practitioners who are not physicians, who cannot perform surgical abortions, or who are unable to diagnose ectopic pregnancies and their complications.

Nor is there reason to believe that systemic bacterial infection is more likely to occur following vaginal, rather than oral, administration of misoprostol. Misoprostol is commonly administered vaginally for the induction of labor without higher reported rates of either intrauterine or systemic infection when compared to orally administered misoprostol or other methods of labor induction. Rather, the occurrence of life-threatening infection in women undergoing a Mifeprex abortion should raise questions about whether prolonged genital tract bleeding in the artificial hormonal milieu created by the Mifeprex Regimen might foster or promote infectious complications. In addition, infection might occur in women who, believing that their abortion is complete and unaware that their uterus actually contains dead tissue, fail to return for follow-up visits.[300] This may be a particular problem when the Mifeprex Regimen is prescribed to adolescents.

The occurrence of a heart attack in a 21 year old woman is always cause for significant concern. A French woman undergoing a mifepristone abortion suffered a fatal heart attack in

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[300] A. Karen Kreutner, M.D., "Postabortion Infections," *Contemporary Ob/Gyn* 1 (2001): at 37-42 (". . . because medical termination may be incomplete in between 3% and 23% of patients, retained tissue and subsequent infection may go unrecognized in those lost to follow up. . . . Some experts fear there will be compliance problems with the third visit, especially when the patient terminates early. In these cases, retained tissue, thought by the patient to be normal bleeding, could lead to endometritis.").

1991. A different prostaglandin (Sulprostone) administered by injection was used in that case.[301] This new case highlights the need for further investigation into a possible causal link between mifepristone-prostaglandin abortions and myocardial infarction.[302]

The ratio of serious adverse events to total uses of the Mifeprex Regimen cannot be ascertained because serious adverse event reporting is likely incomplete and because it is not publicly known how many times the Mifeprex Regimen has been used. Regardless of the relative number of serious adverse events, the nature of these events demands immediate FDA action to prevent future patient injuries and deaths.[303] The Joint Commission on the Accreditation of Healthcare Organizations[304] ("JCAHO" or "Joint Commission") has developed an approach for investigating adverse events similar in gravity to those that prompted the issuance of the Dear Doctor Letter. The JCAHO looks for "sentinel events" which are "unexpected occurrence[s] involving death or serious physical or psychological injury, or the risk thereof."[305] "Sentinel events" *signal* the need for the commencement of a "root cause analysis" of the event(s),[306] with the goal of developing an appropriate administrative response from the health care organization that will prevent the occurrence of future serious adverse events. A root cause analysis of sentinel events is performed before a statistically significant number of injuries or deaths occurs. It seeks to discern the facts surrounding each occurrence, distinguish factors peculiar to individuals from those pointing to procedural or administrative deficiencies, and recommend corrective measures to such systemic failures in the delivery of a particular therapy.

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[301] *See* "Noticeboard: A Death Associated with Mifepristone/Sulprostone," *Lancet* 337 (April 20, 1991): at 969-70 ("A spokeswoman for Roussel-Uclaf SA, the company that manufactures mifepristone, said 'the death was clearly from cardiovascular shock following 'Nalador' (Schering) injection.'").

[302] The Mifeprex Regimen should be contraindicated for women with cardiovascular risk factors until further clinical experience indicates that such contraindication is unnecessary.

[303] Even FDA acknowledged the rarity of the events referenced in the Dear Doctor Letter. With respect to bacterial infection, for example, FDA observed that "the rate of serious infection as a complication of pregnancy is 3.5 per 1000 pregnancies. Uterine infection occurs in 0.1-4.7% of first trimester surgical abortions and in 0.0-6.1% of medical abortions. In the past, it was most often associated with illegal abortions. It rarely occurs with pelvic surgery or even with otherwise normal childbirth." FDA Q & A's, *infra* Appendix A, at Question 3. FDA similarly noted the unusual nature of a heart attack in a young woman: "The single heart attack occurred in a 21 year old. A heart attack in very young women is extremely rare. . . . In 1997, the rate among US women aged 20-24 years was 0.19 per 100,000 women." *See id.* at Question 4.

[304] The Joint Commission "evaluates and accredits nearly 18,000 health care organizations and programs in the United States. An independent, not-for-profit organization, JCAHO is the nation's predominant standards-setting and accrediting body in health care. Since 1951, JCAHO has developed state-of-the-art, professionally based standards and evaluated the compliance of health care organizations against these benchmarks." Joint Commission webpage at: <http://www.jcaho.org/whatwedo_frm.html>.

[305] Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#I. Sentinel Events>.

It is particularly important that FDA react to these sentinel events because the clinical trials underlying the approval of the Mifeprex Regimen did not adhere to FDA's endorsed scientific methodology for such trials. The substandard trial design of the U.S. and French Clinical Trials precluded an accurate estimation of the safety of the Mifeprex Regimen compared to the existing available alternatives. Moreover, FDA did not require the sponsor to conduct rigorous Phase IV studies, which could have compensated for some of these deficiencies by generating additional safety data. The agency has not performed a root cause analysis, but has instead hastily postulated that the vaginal administration of misoprostol is the underlying cause of the adverse events.[307] The Petitioners believe that there are probably more scientifically sound explanations for these adverse events and that the supposed safety of the Mifeprex Regimen has been called into question. The occurrence of the adverse events related to ectopic pregnancies and life-threatening systemic bacterial infections adds significant weight to the concerns of those who have long warned that mifepristone-misoprostol abortions are dangerous. FDA has previously dismissed such concerns but now must respond to the accumulating evidence and act accordingly. Withdrawal of the approval is warranted.[308]

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[306] The Joint Commission defines "root cause analysis" as "a process for identifying the basic or causal factors that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event. A root cause analysis focuses primarily on systems and processes, not individual performance. It progresses from special causes in clinical processes to common causes in organizational processes and identifies potential improvements in processes or systems that would tend to decrease the likelihood of such events in the future, or determines, after analysis, that no such improvement opportunities exist." Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#Root cause analysis>.

H. FDA'S APPROVAL OF MIFEPREX SHOULD BE WITHDRAWN BECAUSE THE SPONSOR IS NOT ENFORCING THE LIMITED RESTRICTIONS ON THE USE OF MIFEPREX

Mifeprex abortion providers openly flout the restrictions included in the approved regimen without any reaction from FDA, Danco, or the Population Council.[309] Shortly after approval, FDA asserted that "[i]f restrictions are not adhered to, FDA may withdraw approval."[310] Subpart H authorizes FDA to withdraw approval of a drug approved under Section 314.520 if "[t]he applicant fails to adhere to the postmarketing restrictions agreed upon."[311] When it adopted Subpart H, FDA explained that "[t]he burden is on the applicant to ensure that

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[307] *See* FDA Q & As, *infra* Appendix A, at Nos. 1, 4, 9, 10, and 11.

[308] The Secretary of HHS is authorized by 21 C.F.R. § 314.530(a) to withdraw approval of a Subpart H drug, subject to the applicant's right to a hearing, if, among other things, "(3) [u]se after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug; (4) [t]he applicant fails to adhere to the postmarketing restrictions agreed upon; (5) [t]he promotional materials are false or misleading; or (6) [o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use."

[309] The absence of a reaction from Danco may not be surprising in light of the cavalier attitude towards the FDA approval process exhibited by Dr. Richard Hausknecht, who is Danco's medical director. As early as July 1994, Dr. Hausknecht, had used methotrexate and misoprostol in clinical tests in the U.S. that Dr. Mitchell Creinin, a prominent abortion researcher, described as "downright unethical" and which Sandra Waldman of the Population Council described as being "very risky." Dr. Hausknecht stopped these experiments in September 1994 when the FDA told him to "stop performing the abortions unless he gets the backing of a medical institution and submits his data and procedures to the FDA for review." Carol Jouzaitis, "Doctor's Abortion-Drug Technique Draws Fire," *Chicago Tribune* (Sept. 12, 1994): at 1 & 14. Dr. Hausknecht admitted, " 'This is a little bit uncharted.' .... But he declared: 'Damn it. I'm not going to wait. This is a step forward. This is important. I want to see this available to women where it's not available now.' " *Id.* In addition, Dr. Hausknecht's website explains step two of the Mifeprex procedure that he employs: "At the conclusion of the [first] visit, the patient receives a packet containing tablets of misoprostol which are to be taken orally or placed in the vagina depending on the regimen you and Dr. Hausknecht choose." Available at: <http://www.safeabortion.com/procedure.htm> (visited July 7, 2002). Both the home use and the vaginal administration of misoprostol contravene FDA's approved regimen.

[310] *See* Letter, Melinda K. Plaisier, Associate Commissioner for Legislation (FDA) to Senator Tim Hutchinson (Oct. 20, 2000): at 2 [FDA FOIA Release: MIF 002648-52].

[311] 21 C.F.R. § 314.530(a)(4).

the conditions of use under which the applicant's product was approved are being followed."[312] FDA should exercise its authority to withdraw its approval for Mifeprex.

Among the common departures from the approved regimen is the practice of offering the Regimen to women with pregnancies beyond seven weeks.[313] The "Mifepristone Medication Guide" directs women not to take Mifeprex if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began." Moreover, women who use the Mifeprex Regimen sign a Patient Agreement, which includes a representation by the patient that "I believe I am no more than 49 days (7 weeks) pregnant.").[314] Thus, the practice of offering Mifeprex to women beyond seven weeks not only contravenes the approved regimen, but it also effectively requires patients to make an untruthful representation in the Patient Agreement. The *Los Angeles Times* explained that, "[B]y offering mifepristone up to the ninth week of pregnancy," Family Planning Associates, "the nation's largest for-profit abortion chain," "obtains a competitive edge over Planned Parenthood, which stays within the seven-week guideline."[315]

In another common deviation from the approved regimen, some abortion providers have eliminated the second of the three prescribed visits. During the initial visit, these providers give the patient misoprostol, typically with instructions to administer it to herself vaginally[316] at home two days later.[317] Yet home administration of misoprostol runs counter to what patients agree to in the Patient Agreement, which states that "I will . . . return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant."[318] The Population Council argued in favor of and FDA considered the benefits of self-administration at home, chief among which is the reduced burden on abortion providers and their facilities, but the agency concluded that these benefits are outweighed by the significant risks to women.[319] The second visit affords the physician the opportunity to monitor the status of the termination[320] and assess the need for misoprostol – tasks which cannot be delegated to the patient.[321] In addition, the second visit enables patients whose abortions are complete to avoid having to take misoprostol.[322]

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[312] *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

[313] Liberty Women's Health Care of Queens, NY, openly acknowledges its use of Mifeprex beyond seven weeks: "While the FDA has approved mifepristone for non-surgical abortions only up to 7 weeks, we use a modified method to extend this period of eligibility in selected patients an additional 14 days up to 9 weeks." Available at: <http://www.abortbypill.com/2.html> (visited Dec. 31, 2001). Likewise, Preterm, an abortion clinic in Cleveland, Ohio, states that abortion using Mifeprex "is effective in terminating pregnancies up to 63 days (9 weeks) from the last normal menstrual period." Available at: <http://www.preterm.org/nonsurg.htm> (visited July 7, 2002).

[314] *See* Item 4 of the Patient Agreement for Mifeprex (mifepristone) Tablets ("Patient Agreement").

[315] Denise Gellene, "RU-486 Abortion Pill Hasn't Caught on in U.S.," *Los Angeles Times* (May 31, 2000): at A1 (quoting Family Planning Associates' official as saying, "You can catch a lot of women in those two [extra] weeks"). Family Planning Associates' website confirmed that the abortion provider offers Mifeprex to women with pregnancies up to nine weeks' gestational age. Available at: <http://www.webworldinc.com/fpamg/abortion_pill.htm> (visited July 7, 2002) ("Medical abortion is limited to patients less than nine weeks pregnant as verified by ultrasound.").

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[316] The likely reason that FDA's approved regimen calls for oral administration is that it is the only mode of administering misoprostol that is currently approved by the FDA. As discussed above, however, the use of misoprostol in conjunction with mifepristone to effect abortions is itself an unapproved indication.

[317] Presidential Women's Center in West Palm Beach, Florida, for example, gives women "four Misoprostol 200 mcg tablets to take home. Forty eight hours after the Mifepristone tablets have been administered the woman moistens four Misoprostol tablets with tap water and inserts them high into her vagina with her fingers." Available at: <http://www.presidentialcenter.com/medical.html> (visited July 7, 2002). *See also*: <http://www.heritageclinic.com/abortion/medical_abortion_pill.htm> (visited July 4, 2002) (Two days after the patient takes mifepristone, she "inserts Cytotec vaginally, which causes the uterus to contract and expel the embryo. This is very similar to the procedure that was FDA approved in 2000 and is approximately 98% effective. **Note:** The FDA approved protocol calls for 3 Mifeprex pills taken orally the first day and 2 Cytotec pills taken orally two days later. However, subsequent studies have show[n] 1 oral Mifeprex and 4 vaginal Cytotec to be as effective with less gastro-intestinal upset."); *see also*: <http://www.fwhc.org/concord/pages/mifepristone.html> (visited July 7, 2002) (Concord Feminist Health Center's web site describes the second phase of the procedure: "In a few days she inserts misoprostol tablets into her vagina. The pregnancy usually ends at home within four hours."); *see also*: <http://www.gynemed.org/ru.html> (visited July 7, 2002) (Gynemed Surgi-Center's web site states: "You will be given two doses of Misoprostol tablets and instructions on how to insert them into your vagina, which you wil[l] do 48 hours after taking RU486."); *see also*: <http://www.hopeclinic.com/medab.htm> (visited July 7, 2002) (Hope Clinic for Women, Ltd. Explains: "You will receive pills, misoprostol ("miss o pross tul") to take home with you. You will be instructed when to use them; they are placed vaginally."). Even the National Abortion Federation, which initiated a nationwide advertising campaign for Mifeprex, sanctions home administration of misoprostol in its "Medical Abortion Start-Up Packet." *See* National Abortion Federation, "Protocol Recommendations for Use of Mifepristone and Misoprostol in Early Abortion," *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 36 ("Home administration of vaginal misoprostol has been found to be safe and effective up to 63 days' gestation and is highly acceptable to patients.").

[318] *See* Patient Agreement, Item 14. *See also* Mifeprex Medication Guide, which explains that on "Day 3 at your provider's office," "your provider will check to see if you are still pregnant," and "[i]f you are still pregnant, take 2 misoprostol tablets."

[319] FDA, which in its 2000 Mifepristone Approvable Letter, agreed to the Population Council's proposal to allow home administration of misoprostol, rejected that option after reconsideration of the issue. *See* Mifeprex Approval Memo, *infra* Appendix A, at 2-3 ("The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the

Danco and the Population Council have not effectively constrained providers of Mifeprex to adhere to the approved regimen. It appears instead that Danco and the Population Council have ignored well-publicized departures from that regimen. Deviations from the approved regimen are particularly troubling because the patient is told to disregard the regimen that she reads about in the Medication Guide and pledges to follow in the Patient Agreement. When a drug is approved under Subpart H, the drug's sponsor is responsible for ensuring compliance

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prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. . . . Returning to the health care provider on Day 3 for misoprostol, as in the U S clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.").

[320] Because of the complications that can arise, periodic monitoring during the termination process is important. For the significant percentage of patients that fail to return for the third visit, the second visit may be the last opportunity for a health care provider to monitor the termination. In the U.S. Clinical Trial, five percent of patients failed to return for the third visit. *See* Medical Officer's Review, *infra* Appendix A, at 10. In other studies, the "loss to follow-up has ranged from three to eleven percent." *See* Spitz Article, *infra* Appendix A, at 1246 (citations omitted). The rate of patients who do not complete the entire regimen in routine clinical practice is likely to be even higher as they will not necessarily be subject to the U.S. Clinical Trial's exclusion criteria, which, among other things, excluded women who were "unlikely to understand and comply with the requirements of the study." Medical Officer's Review, *infra* Appendix A, at 9.

[321] *See* ACOG Practice Bulletin, *infra* Appendix A, at 6 (*citing* Mitchell Creinin, *et al.*, "Methotrexate and Misoprostol for Early Abortion: A Multicenter Trial," *Contraception* 53 (1996): at 321-27) ("Women as well as their practitioners are often unable to judge correctly if the women have aborted by evaluating symptomatology. In clinical trials with methotrexate and misoprostol, only about half of women who thought they had aborted actually had done so."); Beth Kruse *et al.*, "Management of Side Effects and Complications in Medical Abortion," *American Journal of Obstetrics and Gynecology* 183 (2000): S65-375, S73 ("Studies demonstrate that women may be unable to judge correctly on the basis of symptoms whether abortion has occurred.").

[322] For those patients whose abortions are not complete, the benefits of in-clinic misoprostol use would be enhanced if patients were required to spend several hours afterward in the abortion facility, where they would have ready access to pain medication and other medical help even if the abortion does not occur during the observation period. The Population Council persuaded FDA not to include this requirement, which was included in the protocol for the U.S. Clinical Trial. Forty-nine percent of the participants expelled their pregnancies during the four-hour observation period after the administration of misoprostol. *See* Spitz Article, *infra* Appendix A, at 1243. Nevertheless, a post-misoprostol waiting period was likely disfavored because the protracted presence of large numbers of bleeding and cramping women could place a strain on abortion facilities.

with the restrictions included in the approved regimen for use of the drug.[323] The Population Council and Danco have shirked this responsibility. FDA, therefore, should withdraw its approval of Mifeprex.

I. THE U.S. CLINICAL TRIAL FOR MIFEPRISTONE DID NOT MIRROR THE ANTICIPATED CONDITIONS FOR THE ULTIMATE USE OF THE DRUG

As a general rule, "Phase 3 trials are usually [conducted] in settings similar to those anticipated for the ultimate use of the drug."[324] FDA, however, approved a regimen that does not contain important safeguards that were employed in the U.S. Clinical Trial.[325] In the U.S. Clinical Trial, for example, the investigators relied on transvaginal ultrasonography (along with menstrual history and pelvic examination) to confirm the gestational age of each pregnancy.[326] The use of ultrasonography also excluded women with ectopic pregnancies. Moreover, physicians participating in the U.S. Clinical Trial had experience in performing surgical abortions, were trained in the administration of the mifepristone-misoprostol procedure, and had admitting privileges at medical facilities that could provide emergency care and hospitalization.[327] In addition, "[a]ll patients were within one hour of emergency facilities or the facilities of the principle [*sic*] investigator."[328] In the U.S. Clinical Trial, after taking misoprostol, "women were monitored for four hours for adverse events."[329] FDA has not retained these requirements governing physician training, ultrasound, the post-misoprostol waiting period, or physician privileges at facilities that provide emergency care.[330] FDA should not have extrapolated conclusions about the safety and efficacy of FDA's approved regimen from data generated under trial conditions not mirroring the approved regimen. Effectively, therefore, the agency approved a drug regimen that it had not tested.

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[323] *See Subpart H Final Rule*, 57 Fed. Reg. at 58953 ("The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed.").

[324] Bertram G. Katzung, M.D., Ph.D., and Barry A. Berkowitz, Ph.D., "Basic & Clinical Evaluation of New Drugs" in Bertram G. Katzung, ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk: Appleton & Lange, 1989): at 56.

[325] The French Clinical Trials, which were not performed by the Population Council, are not discussed here because they were not conducted for the purpose of supporting the mifepristone NDA and, therefore, were not designed to reflect American conditions of use.

[326] *See* Spitz Article, *infra* Appendix A, at 1242.

[327] "The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and /or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists." Mifeprex Approval Memo, *infra* Appendix A, at 5. Medical Officer's Review,

J. BY WAIVING THE PEDIATRIC STUDY REQUIREMENT, FDA MAY HAVE ENDANGERED THE HEALTH OF ADOLESCENT GIRLS

FDA's approval of Mifeprex violated FDA's regulations, effective April 1, 1999, requiring that new drugs be tested for safety and effectiveness in the pediatric population (collectively, the "*Pediatric Rule*").[331] Requiring data on girls age 18 and under also would have been consistent with the guidelines for trials in the pediatric population that FDA accepted at the

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infra Appendix A, at 6 (The U.S. Clinical Trial was "conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.").

[328] Mifeprex Approval Memo, *infra* Appendix A, at 5. The "one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services." *Id.* FDA contends that concerns arising from the elimination of the geographical proximity rule have "been dealt with through labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated." Mifeprex Approval Memo at 5.

[329] *See* Spitz Study, *infra* Appendix A, at 1242.

[330] The Prescriber's Agreement requires only that the supervising physician be "able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary." By contrast, the protocol for the U.S. Clinical Trial required that the physician have "privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc." Mifeprex Approval Memo, *infra* Appendix A, at 5. The shift in focus from access by the provider of the abortion to access by the woman who has the abortion, attenuated the link between the abortion provider and the emergency care provider, a link that is critical to ensuring that women receive timely emergency care.

[331] *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Final Rule*, 63 Fed. Reg. 66632 (Dec. 2, 1998) (*Pediatric Adopting Release*). The notice of proposed rulemaking was released as: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Proposed Rule*, 62 Fed. Reg. 43900 (Aug. 15, 1997).

International Conference on Harmonization.[332] Nevertheless, in the Mifeprex Approval Letter, FDA stated, "We are waiving the pediatric study requirement for this action on this application."[333] Thus, FDA approved Mifeprex for use without requiring safety and effectiveness testing for the pediatric population.[334]

As FDA noted when it adopted the *Pediatric Rule*, "many of the drugs and biological products that are widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established."[335] FDA observed that "the absence of pediatric labeling information poses significant risks for children."[336] The ICH has noted that adolescence "is a period of sexual maturation; medicinal products may interfere with the actions of sex hormones and impede development."[337] Such hormonal changes may "influence the results of clinical studies."[338] These concerns for the health of infants, children, and adolescents

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[332] *FDA Guidance: E11 Clinical Testing for Pediatric Uses* at 9 and 11 (Heading for Section 2.5.5). FDA, cognizant of the need for such studies, obtained a commitment from the sponsor in 1996 to conduct Phase IV studies to examine the safety and efficacy of the regimen in girls under 18 years of age. FDA subsequently curtailed this Phase IV study requirement when it approved the Mifeprex NDA.

[333] Mifeprex Approval Letter at 3.

[334] The Mifeprex Label accordingly included the standard disclaimer employed in drug labeling when the drug sponsor has not provided sufficient information to support a pediatric use for the drug: "Safety and effectiveness in pediatric patients have not been established."

[335] *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

[336] *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

[337] FDA, "Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population" (Rockville, Md.: Dec. 2000): at 11 (§ 2.5.5) ("*FDA Guidance: E11 Clinical Testing for Pediatric Uses*"). Section 2.5.5 states that the adolescent subgroup should extend from "12 to 16-18 years (dependent on region)." *Id.* at 11-12 (§ 2.5.5).

[338] *See FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 12 (§ 2.5.5). These ICH concerns, quoted below, pertaining to the difficulty of testing drugs in the adolescent population amplify the need for FDA to have required clinical study of the difficulties that might arise when teenage girls undergo the Mifeprex Regimen:

> Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.
>
> Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect

prompted FDA to begin the rulemaking that culminated with the issuance of the *Pediatric Rule*, establishing "a presumption that all new drugs and biologics will be studied in pediatric patients" unless the requirement is waived.[339] More specifically, the *Pediatric Rule* requires that applicants seeking approval for new chemical entities, new biological products, new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration contain safety and effectiveness information on relevant pediatric age groups.[340]

FDA made clear that the Mifeprex NDA was covered by the *Pediatric Rule*.[341] Nevertheless, FDA fully waived the rule for Mifeprex without explanation. Full or partial

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> appearance. In clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol, and tobacco should be specifically considered.
>
> The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centers knowledgeable and skilled in the care of this special population.").

Id. at 12 (§ 2.5.5).

[339] *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 (introduction to "II. Highlights of the Final Rule"). The importance of testing drugs in children was highlighted during the recent controversy surrounding FDA's attempt to suspend the *Pediatric Rule*. FDA's planned two-year suspension came in response to the passage of the Best Pharmaceuticals for Children Act, which offers incentives for manufacturers to test drugs in children. Public Law No. 107-109, 115 Stat. 1408 ("BPCA"). *See also* Association of American Physicians and Surgeons, Inc. v. FDA, Defendants' Motion for Stay of Proceedings, Civil Action No. 00-2898 (HHK) (Mar. 18, 2002). FDA later reversed its position in response to criticism from physicians and members of Congress. FDA's attempt to suspend the *Pediatric Rule* prompted the introduction of identical legislation in the House of Representatives and the Senate to codify the *Pediatric Rule*. *See* S. 2394, 107th Congress, 2nd Session (2002) (co-sponsors: Senators Hillary Rodham Clinton (D-NY), Mike DeWine (R-OH), and Chris Dodd (D-CT)); and H.R. 4730, 107th Congress, 2nd Session (2002) (co-sponsors: Representatives John D. Dingell (D-MI), Henry A. Waxman (D-CA), Rosa DeLauro (D-CT), Anna Eshoo (D-CA) and Sherrod Brown (D-OH)). As Senator Hillary Rodham Clinton, a co-sponsor of the Senate bill explained, "if we want to protect our children over the long term, then we in Congress need to step in and make the Pediatric Rule the law of the land. Short of taking that action, we risk denying children the protection that we require for adults." Press Release, "Senators Will Introduce Legislation to Codify Pediatric Rule" (Apr. 17, 2002) (available at: <http://clinton.senate.gov/~clinton/news/2002/04/2002417811.html>). *See also* Marc Kaufman and Ceci Connolly, "U.S. Backs Pediatric Tests In Reversal on Drug Safety," *Washington Post* (April 20, 2002): at A3.

[340] *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 ("A. Scope of the Rule"), and as required pursuant to 21 C.F.R. § 314.55(a).

[341] The Mifeprex Approval Letter stated: "Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application." Mifeprex Approval Letter at 3. Because the Mifeprex NDA was filed before the Pediatric Rule went

waivers of the pediatric study requirement may be granted either upon request of the applicant or by FDA on its own motion.[342] Both FDA-initiated and sponsor-requested waivers must satisfy certain criteria. FDA is required to grant a full or partial waiver "if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver ... have been met."[343]

Section 314.55 provides three procedural tracks by which an applicant may obtain a waiver of the study requirement. The first requires that two conditions being met:[344] (1)"[t]he drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients," *and* (2) the drug product "is not likely to be used in a substantial number of pediatric patients." With respect to this basis for waiver, FDA has "emphasize[d] that the study requirement applies to a product that offers a meaningful therapeutic benefit even if it is not used in a substantial number of pediatric patients, and vice versa."[345] As noted above, FDA, in connection with its determination to approve Mifeprex under Subpart H, concluded that the Mifeprex Regimen provides a therapeutic benefit over the existing treatment – surgical

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into effect, if a waiver had not been granted, the Population Council would have had until December 2, 2000 to submit "an assessment of pediatric safety and effectiveness." *See Pediatric Adopting Release*, 63 Fed. Reg. at 66658-59 ("V. Implementation Plan").

[342] Although it appears that FDA waived the rule *sua sponte*, FDA should have required the manufacturer to provide certain information to support the waiver. The agency has not released such documents to the public in response to FOIA requests. When it adopted the *Pediatric Rule*, the agency noted: "FDA agrees that the burden is on the manufacturer to justify waivers, but believes that the rule already adequately imposes that burden. The rule requires both a certification from the manufacturer that the grounds for waiver have been met and an adequate justification for the waiver request." *Pediatric Adopting Release*, 63 Fed. Reg. at 66648 (§ 29).

[343] 21 C.F.R. § 314.55(c)(4)("FDA action on waiver.").

[344] 21 C.F.R. § 314.55(c)(2)(i).

[345] *Pediatric Adopting Release*, 63 Fed. Reg at 66635 ("II.D.2. Waiver of the Study Requirement," *see* first paragraph).

abortion.[346] This conclusion by itself precludes FDA from using the first method for granting waiver of the *Pediatric Rule*.[347]

Even if FDA had not judged the Mifeprex Regimen to offer a "meaningful therapeutic benefit," the second requirement for waiver in this first track is not met because Mifeprex can be expected to be used in a "substantial number of pediatric patients," which FDA defines as "50,000 pediatric patients with the disease for which the drug or biological product is indicated."[348] In the *Pediatric Adopting Release*, FDA stated that the "relevant age groups will . . . be defined flexibly."[349] With respect to Mifeprex, it would have been appropriate to classify girls under the age of 18 as pediatric patients because safety and effectiveness in this population had not been studied.[350] If the pediatric population comprises all girls age 17 and under, then we estimate that there were 357,200 pediatric pregnancies per year from 1995 to 1997 in the United States.[351] If the pediatric population comprises all girls age 16 and under, then we estimate that there were a total of 196,520 pregnancies per year from 1995 to 1997.[352] Even if the pediatric population encompasses only girls age 15 and under, we estimate that there were

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[346] *See* Mifeprex Approval Memo at 6.

[347] FDA noted that, for purposes of the *Pediatric Rule*, it would rely "in part, on CDER's current administrative definition of a 'Priority' drug, applied to pediatric populations" to define "meaningful therapeutic benefit." The phrase, "meaningful therapeutic benefit," appears identical in the Subpart H and Priority review contexts. As noted above, Mifeprex was accorded priority review. The modifications to "meaningful therapeutic benefit" for purposes of the *Pediatric Rule* appear to have broadened the scope of the phrase. *See Pediatric Rule*, 63 Fed. Reg. at 66646.

[348] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647.

[349] *Pediatric Rule*, 63 Fed. Reg. at 66634 ("C. Age Groups"). After noting comments to the proposed rule that argued for flexibility in setting age definitions (including a comment arguing for "pediatric patient" to include those "from 0 to 21 years"), FDA stated that "the age ranges identified in the proposal may be inappropriate in some instances" and that it had "deleted the references in the rule to specific age ranges." *Id.* at 66651.

[350] Although FDA acknowledged that the safety and effectiveness of Mifeprex were not studied in girls under age 18 and required a statement to that effect in the labeling, the agency anticipated and even encouraged use in this population when it stated that: "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients." Mifeprex Approval Memo at 7.

[351] *See infra* Appendix B at B-3.

[352] *See infra* Appendix B at B-4.

85,960 pregnancies per year from 1995 to 1997 in this age range.[353] Thus, under any definition of the pediatric population, the 50,000 patient cut-off set forth in the *Pediatric Adopting Release* is exceeded. In sum, *neither* of the requisite conditions for a waiver of the *Pediatric Rule* under the first waiver track provided in Section 314.55 is satisfied.[354]

Second, FDA may also waive the pediatric study requirements if the "necessary studies are impossible or highly impractical because, *e.g.*, the number of such patients is so small or geographically dispersed."[355] FDA explained that "that this ground for waiver [must] be interpreted narrowly":[356]

> Although the number of patients necessary to permit a study must be decided on a case-by-case basis, FDA agrees that there are methods available to conduct adequate studies in very small populations. . . . Because of the speed and efficiency of modern communications tools, geographic dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size. FDA is not persuaded that inability to recruit patients because of parental fears associated with administration of the drug is an adequate basis to conclude that studies are impractical where there is also evidence that similar products are regularly prescribed to pediatric patients outside of clinical trials.[357]

Pediatric Mifeprex studies would not have been either "impossible or highly impractical." As described above and in Appendix B, the population of pediatric females that becomes pregnant each year is large and the female population is evenly distributed throughout the United States. Thus, this second waiver track available under Section 314.55 could not have been satisfied (and FDA apparently has not taken a position to the contrary).

FDA may waive the pediatric study requirement under Section 314.55's third waiver track when "[t]here is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups."[358] As noted above, FDA endorsed the proposition that "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen."[359] Thus, by suggesting that Mifeprex could be used appropriately in the pediatric population, FDA eliminated this third track as a possible basis for waiver.

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[353] *See infra* Appendix B at B-4.

[354] *See* 21 C.F.R. § 314.55(c)(2)(i).

[355] *See* 21 C.F.R. § 314.55(c)(2)(ii).

[356] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

Absent a waiver or deferral, the *Pediatric Rule* requires any drug application to "contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric subpopulations . . . ."[360] FDA is authorized instead to extrapolate such data from adult studies "[w]here the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients."[361] The underlying adult studies, however, must be "adequate and well-controlled."[362] As noted above, the Population Council did not provide evidence from adequate and well-controlled studies as to the safety and effectiveness of Mifeprex in the *adult* population. Reliance on these flawed adult studies for a determination of the safety and effectiveness of Mifeprex in the pediatric population was inappropriate. Furthermore, to assume that the effects of a potent antiprogesterone, mifepristone, and a

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[357] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

[358] 21 C.F.R. § 314.55(c)(2)(iii).

[359] Mifeprex Approval Memo at 7.

[360] 21 C.F.R. § 314.55(a). FDA stated that it was waiving the *Pediatric Rule*. Mifeprex Approval Letter at 3. The agency did not assert that it had made a determination that pediatric studies were not required because the adult trials were sufficient to support extrapolation of conclusions as to safety and effectiveness in the pediatric population. However, because FDA failed to provide any justification for its waiver, it is difficult to determine whether the agency was, in fact, relying on this provision to eliminate the pediatric study requirement for Mifeprex.

[361] *See* 21 C.F.R. § 314.55(a).

[362] *See* 21 C.F.R. § 314.55(a).

powerful prostaglandin analogue, misoprostol, in pregnant adults can be extrapolated to pregnant adolescents, who are still developing physiologically and anatomically, is medically unsound.[363]

FDA violated its own rules when it waived the Pediatric Rule in the face of explicit criteria that necessitated compliance with the rule.[364] Furthermore, FDA offered no explanation for its determination to waive the rule. As FDA's treatment of other drugs illustrates, a waiver would have been appropriate only if Mifeprex had already been tested in children and labeled accordingly, or if the *Pediatric Rule's* criteria for waiver were satisfied.[365] Because FDA waived the study requirement in the face of explicit criteria that appear to prohibit such action in this instance, the agency violated its rule. In addition to violating Section 314.55, FDA's unexplained waiver of the *Pediatric Rule* for the Mifeprex NDA constitutes agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.[366]

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[363] The Mifeprex Regimen acts upon the reproductive system, which changes dramatically during adolescence. Adolescents, for example, could face disruptions in ovulatory function as a result of concentrations of mifepristone in developing ovarian follicles, or other health problems. Moreover, teenagers may face heightened risks arising from decreased compliance with the full regimen, poor recall of their last menstrual period, and their reluctance to tell others about their pregnancies.

[364] Of course, a partial waiver of the study requirement is appropriate for the non-adolescent pediatric sub-groups. *See* 21 C.F.R. § 314.55(c)(3). According to *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses*, the pediatric sub-populations other than "adolescents" are: 1) preterm newborn infants; 2) term newborn infants (0 to 27 days); 3) infants and toddlers (28 days to 23 months); 4) children (2 to 11 years). *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 9 (§ 2.5).

[365] In April 2000, FDA approved a suitability petition for Pamidronate Disodium Injection, 3 mg/mL, 10 mL vials, and 9 mg/mL, 10 mL vials, the listed drug products for which are Aredia (Pamidronate Disodium for Injection), 30 mg/vial and 90 mg/vial, and determined that the "proposed change in dosage form is subject to the Pediatric Rule but that a full waiver of the pediatric study requirement . . . is appropriate." *See* Letter, FDA to Mitchall G. Clark (April 18, 2000): at 1 (Docket No. 00P-0091/CPI) (concluding "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed product in the pediatric population since the necessary studies are impossible or highly impractical because the number of patients is small and geographically dispersed"). *See also* Letter, FDA to The Weinberg Group, Inc. (June 13, 2000): at 1-2 (Docket No. 99P-5447/CPI) (approving a generic manufacturer's petition to file an Abbreviated New Drug Application for Cefaclor Chewable Tablets, 125 mg, 187 mg, 250 mg, and 375 mg, the listed drug products for which are Ceclor (Cefaclor) for Oral Suspension, 125 mg/5mL, 187 mg/5mL, 250 mg/5mL, and 375 mg/5mL because FDA determined that the "proposed change in dosage form is subject to the Pediatric Rule" but "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed products in the pediatric population, because the specific drug products that you reference are adequately labeled for pediatric use").

[366] FDA has required numerous drug sponsors to comply with the *Pediatric Rule*, but it approved Mifeprex without stating its basis for waiving the requirement. *See, e.g.*, Letter, FDA to King & Spalding (June 13, 2000): at 1

K. FDA'S UNEXPLAINED REDUCTION OF THE SPONSOR'S PHASE IV REQUIREMENTS WAS ARBITARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

Not only did FDA improperly and without explanation waive its own pediatric testing requirements, but it also inexplicably narrowed the scope of the Population Council's commitments to conduct post-approval Phase IV studies. As a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects.[367] Phase IV, which occurs after a drug is approved, provides the opportunity to "monitor[ ] the safety of the new drug under actual conditions of use in large numbers of patients."[368] Not only

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(Docket No. 99P-2776/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Oxycodone Hydrochloride and Acetaminophen Oral Solution, 7.5 mg/500 mg per 15 mL, the listed drug product for which is Oxycodone and Acetaminophen Tablets 7.5 mg/500 mg, based on the fact that FDA "has determined that your proposed change in dosage form is subject to the Pediatric Rule and has concluded that investigations are necessary to demonstrate the safety and effectiveness in the pediatric population . . . . Therefore, the Agency concludes that the proposed product should be evaluated for safety and efficacy in the pediatric population."); Letter, FDA to Abbott Laboratories (Sept. 29, 1999): at 1-2 (Docket No. 98P-0821/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Hydromorphone Hydrochloride Injection, 0.2 mg/mL, 30 mL vials, the listed drug product for which is Dilaudid-HP Injection, 10 mg/mL, 5 mL ampoules and 50 mL vials, because the "proposed change in route of administration is subject to the Pediatric Rule," "clinical trials are required for this specific drug product," and "investigations are necessary to demonstrate the safety and effectiveness in the pediatric population").

[367] A.G. Gilman, T.W. Rall, A.S. Nies, P. Taylor, eds., *The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990): at 77 ("Although assessment of risk is a major objective of [clinical trials], this is far more difficult than is the determination of whether a drug is efficacious for a selected condition. Usually about 500 to 300 carefully selected patients receive a new drug during phase-3 clinical trials . . . . Thus, the most profound and overt risks that occur almost immediately after the drug is given can be detected in a phase-3 study, if these occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing. It is thus obvious that a number of unanticipated adverse and beneficial effects of drugs are only detectable after the drug is used broadly.").

[368] Bertram G. Katzung, M.D., ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk, CT: Appleton & Lange, 1989): at 56. "Final release of a drug for general prescription use should be accompanied by a vigilant postmarketing surveillance program. The importance of careful and complete reporting of toxicity after marketing approval by the FDA can be appreciated by noting that many drug-induced effects have an incidence of 1:10,000 or less. . . . Because of the small numbers of subjects in phases 1-3, such low-incidence drug effects will not generally be detected before Phase 4, no matter how carefully the studies are executed. Phase 4 has no fixed duration." *Id.* at 56-7.

did FDA approve the NDA on the basis of clinical trials so defective with respect to their design and execution as to render them insufficient to establish short-term safety and effectiveness, but FDA also permitted the Population Council to substantially pare down the Phase IV trials that it would perform.

In response to an FDA request, on September 16, 1996, the Population Council agreed to conduct a set of Phase IV studies.[369] FDA "reminded" the Population Council of these commitments in both the 1996 and 2000 Approvable Letters.[370] The Population Council agreed to perform studies with the following objectives:

1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.
6. To ascertain the effect on children born after treatment failure.[371]

These studies would have addressed some of the health issues that were not evaluated during pre-approval testing.

The Mifeprex Approval Letter released on September 28, 2000, however, contains only two Phase 4 study obligations, a radical curtailment of the earlier commitments.[372] The letter stated that "the following Phase 4 commitments, specified in [the Population Council's] submission dated September 15, 2000 . . . *replace all previous commitments* . . . ."[373]

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[369] FDA made its request on August 22, 1996, after it had received Phase IV study recommendations from the FDA Advisory Committee. *See* Medical Officer's Review, *infra* Appendix A, at 20-24.

[370] *See* 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

[371] 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

[372] *See* Mifeprex Approval Letter, *infra* Appendix A, at 2-3.

> (1) "A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention."[374]
>
> (2) "A surveillance study on outcomes of ongoing pregnancies."[375]

FDA stated that "[p]revious study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms."[376] The agency, thus, compounded its failure to require the Population Council and Danco to comply with the strictures of the Pediatric Rule when it permitted them to consider the effect of the Mifeprex Regimen on patients under 18 as part of another study rather than as a separate Phase IV study.[377] The Approval Letter explained that

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[373] Mifeprex Approval Letter, *infra* Appendix A, at 2.

[374] Mifeprex Approval Letter, *infra* Appendix A, at 3. The Population Council acknowledged three weaknesses of this study. First, the sample size would be limited so that the sponsor "will only be able to determine whether the combined safety rates of hospitalizations, medically necessary surgical interventions, and IV fluids in each of the two cohorts are within plus or minus 5 percentage points of the expected 2% rate. We will not be able to detect differences of individual safety outcomes such as blood transfusions and deaths." *See* Amendment 062 to the NDA, Revised Materials (Sept. 19, 2000): at 3. [FDA FOIA Release: MIF 007896-7903]. Second, the Population Council predicted that it might have difficulty finding women who were referred to another provider for care. *Id.* at 3-4. Third, it might be difficult to find women who did not return for their follow-up visit. *Id.* at 4. These three study weaknesses appear, at least in part, to stem from faulty selection criteria for study subjects. Patients should not be enrolled in a study unless they are willing to comply with follow-up visits and telephone inquiries. Additionally, informed consent forms authorize investigators to request medical records from other health care providers.

[375] Mifeprex Approval Letter, *infra* Appendix A, at 3.

[376] Mifeprex Approval Letter, *infra* Appendix A, at 3. These issues were characterized by the sponsor as "Secondary Study Objectives." *See* Amendment 062 to the NDA (Sept. 19, 2000): at 1. The failure to consider each issue in a separate study is likely to compromise the quality of the data generated. Because the study is primarily focused on a provider-level variable (ability to provide surgical intervention), the study will not necessarily yield a meaningful sample size for each of the relevant patient-level variables (age and smoking status). Patients will be enrolled "consecutively from each provider until the provider's quota is met." *See id.* at 2.

[377] The Population Council submitted data from the Spitz Study on 106 women age 35 and older and 51 patients under age 20. *See* Mifeprex Approval Letter, *infra* Appendix A, at 7. However, the effects and potential age-specific risks of the Mifeprex Regimen on women outside the tested age range deserve separate consideration in studies with far more subjects. Approximately 279,000 girls nineteen and younger and more than 84,000 women over the age of 35 obtain abortions in the United States annually. *See* Appendix B, *infra*, at B-4 (§§ 5 and 6). The Mifeprex Regimen, which directly interacts with the reproductive system, could conceivably interfere with pubertal development, as discussed above, and might pose unique risks to women who are nearing the end of their reproductive years.

"the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996."[378]

It appears, however, that the modifications came largely in response to the Population Council's unwillingness to explore the ramifications of the Mifeprex Regimen. On August 18, 1999, the Population Council acknowledged its Phase IV commitments, but stated that "[w]e plan to discuss in more detail and develop a consensus with the FDA post-NDA approval."[379] The Population Council complained, for example, that "[a] prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades."[380] Similarly, the Population Council informed FDA that it was "not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing this, as it could violate women's privacy."[381] The Population Council's concerns about privacy lack merit. Patients who participate in clinical trials give their consent to participate and to be monitored, thus eliminating concerns about privacy. Similarly, FDA should not have accorded undue weight to the Population Council's protestations about the potential expense of the trials; drug sponsors, who stand to profit from a drug's sales, are responsible for bearing the expenses incurred in establishing the safety and efficacy of a drug.[382]

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[378] Mifeprex Approval Memo, *infra* Appendix A, at 7. FDA's conclusion that the reduction to only two Phase IV studies "reflect[s] current postmarketing questions" ignores a number of issues about Mifeprex that remain unexplored. Because mifepristone interferes with pregnancy by binding to the progesterone receptor in the placenta, there is concern that the drug may affect not only the uterus, but the brain, breasts, adrenal glands, ovaries, and immune cells, all of which also have progesterone receptors. Concerns that mifepristone may have a carcinogenic effect on breast tissue have also been expressed. *See, e.g.,* Testimony of Dr. Joel Brind, FDA Hearings Transcript, *infra* Appendix A, at 172-175. Mifepristone also could affect the pituitary gland, the adrenal glands, and immune cells, all of which have glucocorticoid receptors. In addition, it is unclear whether a woman who undergoes multiple mifepristone-misoprostol abortions could suffer adverse effects. *See* ACOG Practice Bulletin, *infra* Appendix A, at 9 ("No well-designed prospective studies address the issue of repeat medical abortion."). Questions also remain about possible effects on the children born to women who have terminated a previous pregnancy with the Mifeprex Regimen. *See, e.g.,* P. Van der Schoot and R. Baumgarten, "Effects of Treatment of Male and Female Rats in Infancy with Mifepristone on Reproductive Function in Adulthood," *Journal of Reproduction and Fertility* 90 (1990): 255-66 (finding that rats exposed to mifepristone in their infancy suffered infertility in adulthood)[FDA FOIA Release: MIF 007165- 007176].

[379] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999).

[380] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999); *see also* Mifeprex Approval Memo at 7 (agreeing with the Population Council's reasoning).

FDA's acquiescence in the Population Council's reduction in its Phase IV commitments compounded the Agency's earlier failure to require the sponsor to conduct clinical trials in accordance with the requirements of Section 314.126 of FDA's rules. FDA's inadequately justified curtailment of the sponsor's Phase IV study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.

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[381] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999). The necessity of long-term monitoring is particularly critical to compensate for the unusually short tracking periods employed in the U.S. Clinical Trial, in which investigators generally did not track patients after their third visit. *See* Spitz Article, *infra* Appendix A, at 1242. "Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted." *Id.* Five percent of the participants in the U.S. Clinical Trial were not tracked through the third visit (which would have occurred on Day 15) because they failed to return for it, suggesting that each of these women was last seen on Day 3, only 2 days after the initial administration of mifepristone. *See* Medical Officer's Review, *infra* Appendix A, at 10. Abbreviated follow-up periods run counter to ICH standards, which state that in clinical trials of drugs intended for use during pregnancy, "followup of the pregnancy, fetus, and child is very important." *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.1.4.3) ("Special populations").

[382] In fact, the sponsors of Mifeprex received substantial outside funding to support their efforts. *See* "Mifepristone: FDA Approval Imminent, Advocates Predict," *Kaiser Daily Reproductive Health Report* (Sept. 28, 2000) (available at: <http://www.kaisernetwork.org/reports/2000/09/kr000928.3.htm>) ("Danco Laboratories, LLC, a small New York-based company, will market the drug with funding from billionaire financier Warren Buffet and hedge-fund czar George Soros and a $10 million loan from the David and Lucile Packard Foundation."); Sharon Bernstein, "Persistence Brought Abortion Pill to U.S.," *Los Angeles Times* (Nov. 5, 2000): at A1 ("The Population Council raised $16 million from like-minded foundations, including the Open Society Institute of New York, which is the philanthropic arm of billionaire George Soros, and the California-based Kaiser Family Foundation.").

IV. PETITIONERS SEEK LEAVE TO AMEND

The Petitioners respectfully inform FDA that they may file amendments to this Petition as information becomes available from Freedom of Information Act requests made before the filing date of this document.[383]

V. CONCLUSION

For the foregoing reasons, the Petitioners respectfully request that the Commissioner immediately enter an administrative stay to halt any further distribution and marketing of Mifeprex until final agency action is taken on this Petition. The Petitioners also respectfully request that the Commissioner revoke approval of Mifeprex for the medical termination of pregnancies less than 49 days' gestation. On the basis of the evidence presented above, the Petitioners respectfully request a full FDA audit of the French and U.S. Clinical Trials.[384]

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[383] The Petitioners have filed numerous Freedom of Information Act ("FOIA") requests with FDA that remain unanswered, including: 1) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of FDA's letter to the Population Council dated, or mailed, on or about June 1, 2000, along with any attachments, appendices, and other accompanying materials"); 2) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of the new drug application . . . filed . . . on or about March 18, 1996 (NDA 20-687)"); 3) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Sept. 14, 2001) (seeking a copy of data submitted by the sponsor "related to the use of mifepristone by women over the age of thirty-five, females under the age of eighteen, and women who smoke" and of the Phase IV study protocols submitted by the Sponsor and any Phase IV trial data); and, 4) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Feb. 6, 2002) (seeking a correct listing of all drug applications approved pursuant to 21 C.F.R. § 314.520 and documents detailing FDA's reasoning for approving drugs under this section of its rules).

[384] An audit of the U.S. Clinical Trial is additionally warranted because of an unusual data management decision made by the Population Council with the apparent approval of the FDA:

> Thank you for speaking with me the other day about our data dilemma. In response to our conversation, we have decided to create two versions of our electronic database from the mifepristone study. The first will reflect exactly the physical copies of the patient record forms, and will be used as the basis for our regulatory submissions to you. The second version will closely match the first, particularly on safety and efficacy indicators, but certain variables will be modified to create an internally consistent database that we can use easily for our planned scholarly publications on the topic. We will keep careful track of the changes we make and we will be able to explain them to an FDA auditor should the need arise. One result

VI. ENVIRONMENTAL IMPACT

This Petition for withdrawal of approval of an NDA is categorically excluded under 21 C.F.R. § 25.31(d). An environmental impact statement is, thus, not required.

VII. ECONOMIC IMPACT

The Economic Impact information shall be submitted only when and if requested by the Commissioner following review of the Petition, in accordance with 21 C.F.R. § 10.30.

CERTIFICATIONS AND SIGNATURES

On behalf of the petitioner organizations listed below, we the undersigned hereby certify that, to the best of petitioners' knowledge, this Citizen Petition is true and accurate. It includes all available information relevant to this Petition, including information both favorable and unfavorable to Petitioners' position in this matter.

So executed this ____ day of August 2002.

Donna Harrison, M.D.
Chairperson, Subcommittee on Mifeprex
American Association of Pro-Life
Obstetricians and Gynecologists
P.O. Box 414
Eau Claire, MI 49111
Phone: (616) 921-2513

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of this approach to handling the data is that certain aspects of our future publications may differ from tabulations that appear in our regulatory submissions.

Letter, Charlotte Ellertson, Population Council, to [Redacted], FDA/CDER (July 28, 1997): at 1 [FDA FOIA Release: MIF 006489].

So executed this ____ day of August 2002.

/S/________________________
Gene Rudd, M.D.
Associate Executive Director
Christian Medical Association
P.O. Box 7500
Bristol, TN 37621
Phone: (423) 844-1000

So executed this ____ day of August 2002.

/S/________________________
Sandy Rios, President
Concerned Women for America
1015 Fifteenth Street, N.W.
Suite 1100
Washington, D.C. 20005
Phone: (202) 488-7000

Exhibit A: Selected Bibliography

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----------. Center for Drug Evaluation and Research, Reproductive Health Drugs Advisory Committee. *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy* (July 19, 1996)("*FDA Hearings Transcript*")[FDA FOIA Release: MIF 005200-90].

----------. Letter, FDA/CDER to Ann Robbins, Population Council (Sept. 18, 1996)("1996 Mifepristone Approvable Letter").[4]

----------. *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)("*FDA Effectiveness Guidance*").[5]

----------. "Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments,"(Jan. 27, 2000) ("Medical Officer's Review").[6]

----------. Letter, FDA/CDER to Sandra P. Arnold, Population Council (Feb. 18, 2000)("2000 Mifepristone Approvable Letter").[7]

----------. Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000) ("Mifeprex Approval Letter").[8]

----------. Memorandum to NDA 20-687 MIFEPREX (mifepristone) Population Council (Sept. 28, 2000) ("Mifeprex Approval Memo").[9]

----------. "Mifepristone Questions and Answers 4/17/2002." (Apr. 17, 2002)("FDA Q & As").[10]

----------. "NDAs Approved under Subpart H," FDA webpage;[11] and, "NDA Supplements Approved under Subpart H," FDA webpage.[12]

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[1] The FDA documents are listed chronologically.

[2] Available at: <http://www.fda.gov/cder/fedreg/fr19921211.txt>.

[3] Available at: <http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf>.

[4] Available at: <http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_approvableltr.pdf>.

[5] Available at: <http://www.fda.gov/cder/guidance/1397fnl.pdf>.

[6] Available at: <http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf> and <http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P2.pdf>.

[7] Available at: <http://www.fda.gov/cder/foi/appletter/2000/20687approvable00.pdf>.

[8] Available at: <http://www.fda.gov/cder/foi/appletter/2000/20687appltr.pdf>.

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[11] Available at: <http://www.fda.gov/cder/rdmt/accapp.htm>. The most recently available version of the chart is reproduced in Appendix C.

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ICH E9:

FDA. "International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials; Availability." *Notice*, 63 Fed. Reg. 49583 (Sept. 16, 1998)(*FDA Guidance (ICH:E9): Statistical Principles*).[17]

ICH E10:

FDA. "Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials." Rockville, Md.: May 2001 ("*FDA Guidance (ICH:E10): Choice of Control Group*").[18]

ICH E11:

FDA. "Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population." Rockville, Md.: Dec. 2000 ("*FDA Guidance: E11 Clinical Testing for Pediatric Uses*").[19]

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[13] Available at: <http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf>.

[14] "ICH" is an abbreviation for: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH efficacy documents are posted at: <http://www.ifpma.org/ich5e.html >.

[15] FDA's version of ICH documents may be found at: < http://www.fda.gov/cder/guidance/index.htm > under "ICH" (left-hand column), then "Efficacy."

[16] FDA's posting of "E8" (Fed. Reg. version) is available at: <http://www.fda.gov/cder/guidance/1857fnl.pdf >.

[17] FDA's publication of "E9" is available at: <http://www.fda.gov/cder/guidance/ICH_E9-fnl.PDF >.

[18] FDA's publication of "E10" is available at: <http://www.fda.gov/cder/guidance/4155fnl.pdf >.

[19] FDA's publication of "E11" is available at: <http://www.fda.gov/cder/guidance/4099FNL.PDF>.

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Appendix B: Statistics Used in This Petition

This Appendix describes the method used to derive several statistics used in this petition. Those statistics are: 1) the total number of abortions that occur in the United States annually for all women and girls; 2) the proportion of women receiving abortions annually in the United States at or before 7 weeks of gestation; 3) the rate at which ectopic pregnancies occur in the United States; 4) the number of pregnancies that occur in the United States in the pediatric population; 5) the number of legal abortions obtained by women age thirty-five and older; and, 6) the number of legal abortions obtained by females 19 and younger. Because statistics vary from year to year, this Appendix averages the last three years of available data. This Appendix rounds to the nearest thousand the figures that describe the quantities of pregnancies or abortions in any particular year. Unless otherwise noted, the data have been obtained from the *Morbidity and Mortality Weekly Report* (*MMWR*), which is published by the Centers for Disease Control (CDC).

1. Total Number of Abortions in the U.S. annually. According to the latest CDC Surveillance Summary on abortion, the number of legal abortions in 1997 was 1,186,039; in 1996 – 1,221,585; in 1995 – 1,210,883.[1] Thus, the average number of abortions per year (rounded to the nearest thousand) is approximately 1,206,000.

2. Proportion of Abortions performed at or before 7 weeks of gestation. According to the 1997 Abortion Surveillance, 35.7% of abortions occurred at or before the 7th week of gestation in 1997.[2] According to the 1996 Abortion Surveillance, 33.8% of abortions occurred at or before the 7th week of gestation in 1996.[3] According to the 1995 Abortion Surveillance, 32.8% of abortions occurred at or before the 7th week of gestation in 1995.[4] Thus, the average proportion of abortions that occurs at or before the 7th week of gestation is 34.1%.

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[1] Centers for Disease Control and Prevention, "Abortion Surveillance – United States, 1997," *Morbidity and Mortality Weekly Report* (*MMWR*) 49 (No. SS-11) (Dec. 8, 2000): Table 2 at 19 ("1997 Abortion Surveillance," previous years will be named similarly).

[2] 1997 Abortion Surveillance at Table 17 at 42 (17.6% for less than or equal to six weeks; 18.1% for the 7th week only).

3. Ectopic Pregnancy Rate. Ectopic pregnancy is the leading cause of pregnancy-related death during the first trimester. In 1995 CDC released its first report documenting "the incidence of ectopic pregnancy by including information about patients managed and treated on an outpatient basis."[5] Previously, CDC tabulated only those ectopic pregnancies treated during a hospitalization. The ectopic pregnancy rate in the United States in 1992 was estimated to be 19.7 per 1000 reported pregnancies based on this new methodology, 2.0% after rounding.[6] FDA recently confirmed an ectopic pregnancy rate of 2.0%.[7] This figure, however, is likely to have increased since 1992, the last year for which CDC reported ectopic pregnancy rates.[8]

4. Pregnancy in the Pediatric Population.[9] Each year in the United States 800-900,000 girls and young women under age 19 become pregnant.[10] CDC states that for girls 14 and under there were 26,600 pregnancies in 1995, 25,400 in 1996, and 23,700 in 1997.[11] Averaging these three years, there are 25,200 pregnancies per annum in the United States among girls under age 15.[12]

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[3] Centers for Disease Control and Prevention, "Abortion Surveillance – United States, 1996," *Morbidity and Mortality Weekly Report* (*MMWR*) 48 (No. SS-4) (July 30,1999): Table 17 at 40 (16.4% for pregnancies less than or equal to six weeks; 17.4% for the 7th week only).

[4] Centers for Disease Control and Prevention, "Abortion Surveillance – United States, 1995," *Morbidity and Mortality Weekly Report* (*MMWR*) 47 (No. SS-2) (July 3, 1998): Table 17 at 66 (15.7% for pregnancies less than or equal to six weeks; 17.1% for the 7th week only).

[5] Centers for Disease Control and Prevention, "Ectopic Pregnancy – United States, 1990-1992," *Morbidity and Mortality Weekly Report* (*MMWR*) 44 (No. 3) (Jan. 27, 1995): at 46-48.

[6] Centers for Disease Control and Prevention, "Ectopic Pregnancy – United States, 1990-1992," *Morbidity and Mortality Weekly Report* (*MMWR*) 44 (No. 3) (Jan. 27, 1995): at 46.

[7] *See* FDA, "Mifepristone Questions and Answers" (Apr. 17, 2002) (available at: <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm#2>) ("An ectopic pregnancy is any pregnancy that develops outside of the womb. It occurs in 2% of all pregnancies.")

[8] The rate of ectopic pregnancies appears to have increased dramatically between 1970 and 1992, which CDC found to be "consistent with the trend in increased prevalence of important risk factors for ectopic pregnancy, including chlamydia and other sexually transmitted infections [note], induction of ovulation, and tubal sterilization [note]." *See id.* at Figure 1 ("Number of ectopic pregnancies – United States, 1970-1992") and at 47 ("Editorial Note").

[9] FDA did not precisely delineate the upper bound of the pediatric population in 21 C.F.R. § 314.55 and the related rulemaking.

According to CDC, among girls age 15 through 17 there were 342,100 pregnancies in 1995, 332,500 in 1996, and 321,300 in 1997.[13] Averaging these three years, there are approximately 332,010 pregnancies per annum in the United States for girls age 15 through 17. If one defines the pediatric population as comprising all individuals under age 18, then there were 357,200 pregnancies per year from 1995-1997.[14]

CDC does not break down pregnancy figures for each year within the 15-17 range. CDC abortion statistics, however, can form a basis for extrapolating the number of pregnancies among girls age 15, 16, and 17. In 1997 girls age 15 obtained 6.8 percent, girls age 16 obtained 12.4 percent, and girls age 17 obtained 18.0 percent of all abortions performed on females age nineteen and under.[15] Assuming that the proportion of pregnancies among 15, 16 and 17 year olds corresponds to the proportion of girls obtaining abortions in that age group in 1997,[16] there were approximately 60,760 pregnancies among girls age 15, 110,560 among girls age 16, and 160,690 among girls age 17.

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[10] Centers for Disease Control and Prevention, "National and State-Specific Pregnancy Rates among Adolescents – United States, 1995-1997," *Morbidity and Mortality Weekly Report* (*MMWR*) 49 (No. 27) (July 14, 2000): at 605-611, 605.

[11] *Id.* at Table 1 at 606.

[12] This Appendix will follow the convention employed by CDC of rounding to the nearest 100.

[13] *Id.* at Table 1 at 606.

[14] That is: 25,200 (14 and under) + 332,200 (ages 15-17) = 357,400 pregnancies per annum (ages 17 and under).

[15] Centers for Disease Control and Prevention, "Abortion Surveillance – United States, 1997," *Morbidity and Mortality Weekly Report* (*MMWR*) 49 (No. SS-11) (Dec. 8, 2000): Table 5 at 25-26 ("Reported legal abortions obtained by adolescents, by known age and state of occurrence – selected states, United States, 1997"). The numbers in this table reflect data collected in 44 states and the District of Columbia.

[16] This would constitute a ratio of 6.8: 12.4: 18.0 or 18.3% (age 15): 33.3% (age 16): 48.4% (age 17).

Therefore, if the pediatric population is limited to girls age 15 and under, there were approximately 85,960 pregnancies per year from 1995-1997.[17] If girls age 16 are included, there were approximately 196,520 pregnancies among the pediatric population per year from 1995-1997.[18] Finally, if the pediatric population encompasses all individuals age 17 and under, then there were approximately 357,210 pregnancies per year from 1995-1997 in the United States.[19]

5. Legal Abortions Obtained by Women Thirty-five and Older. According to recent CDC Surveillance Summaries on abortion, the number of legal abortions obtained by women age 35 and older in 1997 was 86,704;[20] in 1996 – 87,787;[21] and, in 1995 – 79,550.[22] Thus, the average number of abortions per year performed on women 35 and older is approximately 84,680.

6. Legal Abortions Obtained by Females 19 and Younger. According to the U.S. Census Bureau, the number of induced abortions in females age 19 years and younger was 274,000 in 1996, 275,000 in 1995, and 288,000 in 1994.[23] Thus, the average number of abortions per year performed on females age 19 years and younger is approximately 279,000.

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[17] That is: 25,200 (14 and under) + 60,760 (age 15) = 85,960 pregnancies per annum (ages 15 and under).

[18] That is: 85,960 (15 and under) + 110,560 (age 16) = 196,520 pregnancies per annum (ages 16 and under).

[19] That is: 25,200 (14 and under) + 332,010 (ages 15-17) = 357,210 pregnancies per annum (ages 17 and under).

[20] *See* 1997 Abortion Surveillance, Table 4 at 24 (65,908 abortions to women age 35 to 39 + 20,796 abortions to women 40 and older).

[21] *See* 1996 Abortion Surveillance, Table 4 at 22 (67,092abortions to women age 35 to 39 + 20,695abortions to women 40 and older).

[22] *See* 1995 Abortion Surveillance, Table 4 at 47 (61,052 abortions to women age 35 to 39 + 18,498 abortions to women 40 and older).

[23] *See* U.S. Census Bureau, *Statistical Abstract of the United States: 2001*, Table 85 at 68.

Mr. SOUDER. Professor Snead.

STATEMENT OF O. CARTER SNEAD, ASSOCIATE PROFESSOR, UNIVERSITY OF NOTRE DAME LAW SCHOOL, AND FORMER GENERAL COUNSEL FOR THE PRESIDENT'S COUNCIL ON BIOETHICS

Mr. SNEAD. Thank you very much. Thank you, Chairman Souder, Ranking Member Cummings, Ranking Member Waxman, Congresswoman Schmidt. Thank you very much for inviting me today to discuss the legal dimensions of this question, which I think are not controversial and not contentious despite the contentious nature of the underlying issue that we are discussing.

In my written comments, I lay out for the committee the various regulatory options that the FDA would have and also that the Secretary of Health and Human Services would have if they were to decide that the circumstances warranted intervention in this matter beyond the changing in labeling and the public health advisories that have already been undertaken.

The central conclusion that I reach in my written testimony is that the FDA is well equipped to respond forcefully to the concerns raised by the co-panelists today regarding the safety of Mifepristone should it decide that such a response is warranted, and I focus on three principal mechanisms in my written testimony that are available both to the FDA and to the Secretary of Health and Human Services. In my oral testimony, I am going to focus on the one mechanism that is unique to Mifepristone given the circumstances of its approval, that is to say under Subpart H, which has received some discussion today already.

Subpart H was devised by the FDA to permit the approval of drugs intended to treat serious or life-threatening illnesses where such drugs imposed a greater-than-normal acceptable risk to the patient. That is, Subpart H was designed in part as an alternative means of approval for useful drugs that would otherwise fail the traditional risk-benefit calculus required for FDA approval. Subpart H facilitated approval of such drugs by imposing additional post-marketing restrictions above and beyond what was required in the normal mechanisms of approval, as has been mentioned by numerous panelists.

These post-market restrictions are absolutely crucial both in terms of their effectiveness and in terms of compliance with those restrictions if the mechanism of Subpart H is to serve its purpose. As the FDA has said in its own final rule, and I am quoting from the final rule, “For drugs approved under the accelerated procedure regulations, the risk-benefit assessment is dependent upon the likelihood that post-marketing restrictions will enable safe use.”

Most important for present purposes, it is clear that Subpart H provides a mechanism for expedited withdrawal of approval upon a finding that the post-marketing restrictions are either ineffective or are not being observed by the manufacturer. As the FDA noted in its final rule also, if the restrictions do not lead to safe use, the risk-benefit assessment for these drugs changes significantly. FDA believes that if that occurs, rapid withdrawal of approval as set forth in this rule is important to the public health.

So this is a unique mechanism, and as the representatives and former representatives of the FDA have noted already, Subpart H is intended to facilitate the move to market of drugs through the imposition of these additional post-market restrictions. It is not difficult to see the implications of Subpart H for the case of Mifepristone.

Danco Laboratories benefited from these unique approval regulations, the cost of which was a promise to comply with the post-market restrictions that the FDA thought appropriate under the circumstances. Thus, if the FDA—and I formulate this as a conditional because I am not privy to any facts that would go to this conclusion, this is a judgment that would have to be made based upon an evaluation of Danco's behavior—if, in fact, the FDA were to conclude that Danco was not in compliance with these post-market restrictions, or alternatively that the post-market restrictions themselves were not effective to render the drug safe for its approved use, then the FDA would be within its authority to withdraw approval following notice and an opportunity for hearing for the drug itself.

And, in fact, it would be difficult to imagine that if FDA did come to that conclusion, that they would not regard it as its duty to withdraw approval, because in the absence of effective post-market restrictions, Mifepristone would presumably not be able to satisfy the statutory criteria for safety. If this were not the case, Mifepristone would have been approved under the traditional provisions rather than under Subpart H.

So essentially, among the mechanisms that I discuss in my written testimony, Subpart H provides a unique opportunity for the FDA to maintain control over the use of Mifepristone, and if under its own inquiries the FDA finds that the post-marketing restrictions are not effective or are not being observed, then the truncated and expedited withdrawal provisions would be activated and FDA would be fully authorized to withdraw approval.

As has been suggested, I agree, I think FDA would have the obligation to answer any open questions regarding the efficacy of the post-market restrictions and also to answer—to inquire about and answer any questions and respond appropriately to any concerns regarding Danco's compliance with the post-marketing restrictions.

Thank you very much.

Mr. SOUDER. Thank you.

[The prepared statement of Mr. Snead follows:]

Testimony
Before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources
Committee on Government Reform
United States House of Representatives

RU-486: Demonstrating a Low Standard for Women's Health?

Statement of

O. Carter Snead

Associate Professor, University of Notre Dame Law School

For Release on Delivery
Expected at 2:00 p.m.
Wednesday, May 17, 2006

Good afternoon Chairman Souder, Ranking Member Cummings, and distinguished Members of the Subcommittee. Thank you for the opportunity to testify today on such an important matter. Even though the underlying subject of today's hearing is quite contentious, my remarks this afternoon should be fairly straightforward and noncontroversial. My charge is quite narrow. My aim is simply to articulate for the Members the options available to the Food and Drug Administration should it decide that the circumstances discussed by my co-panelists today warrant further regulatory intervention beyond the previous labeling changes and public health advisory issued in connection with safety concerns regarding RU-486 ("mifepristone").

My remarks today are entirely my own. They are also prospective in nature; that is, I will not speak about the highly unusual and irregular circumstances under which mifepristone was approved.[1] Finally, my remarks are essentially descriptive rather than normative. That is, I am here to describe to the Committee what the FDA is empowered to do as a matter of law, should it decide to intervene. I take no position on the wisdom of intervention or non-intervention in this particular case. That policy question turns in the first instance on an *empirical* judgment about the safety and efficacy of mifepristone in light of the scientific and medical evidence. I am not in a position to make such a judgment. Moreover, the FDA's decision in this matter crucially depends on certain facts to which I am not privy, namely, facts relating to Danco Laboratories' compliance (or noncompliance) with the strictures imposed on it by the FDA pursuant to the special regulations under which its product was initially approved.

The central animating purpose of the Food and Drug Administration is to protect the public from unsafe articles and products within its jurisdiction. I do not believe this to be a controversial proposition. It is not surprising, therefore, that the enabling statutes and regulations administered by FDA provide it with the clear authority to withdraw the approval of drugs that are revealed to be unsafe. No power could be more fundamental to the FDA's chief function of ensuring public safety.

The FDA is thus well-equipped to respond forcefully to the concerns raised by my co-panelists today regarding the safety of mifepristone, should it choose decide that such a response is warranted. It has substantial powers granted to it by the unique regulations pursuant to which mifepristone was approved (so-called Subpart H).[2] It likewise enjoys signficant authority under its traditional withdrawal provisions, found both in the Food, Drug, and Cosmetic Act, Section 505(e) and relevant regulations.[3] Finally, the Secretary of Health and Human Services enjoys the non-delegable authority to declare an "imminent hazard" in connection with mifepristone, should he decide that this is appropriate under the circumstances.[4] I will take each in turn. Before doing so, however, I should point out that the FDA most often achieves its ends in this context through *informal* means. That is, by persuading drug companies that it is in their enlightened self-interest to voluntarily surrender their approval for drugs that are shown to be unsafe. The present circumstances involving Danco, however, may present the rare exception to this rule. That is, it has been reported that Danco's only product is Mifeprex (its brand name for mifepristone).[5] Thus, it is not likely to be moved by the typical considerations that spur companies into voluntary compliance, namely, concerns regarding its future dealings with the FDA on additional products. As such, should the FDA seek to withdraw approval for mifepristone, it may have no choice but to invoke its formal coercive authorities described below.

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[1] For an excellent overview of the approval process for RU-486, see Lars Noah, "A Miscarriage in the Drug Approval Process?: Mifepristone Embroils the FDA in Abortion Politics," 36 *Wake Forest Law Review* 571 (2001).

[2] 21 CFR 314.500 *et seq*

[3] 21 U.S.C. 355(e), and 21 CFR 314.150.

[4] *See id.*

Withdrawal Provisions of Subpart H

In the face of the widespread criticism that FDA's approval mechanisms were too onerous to quickly move innovative drugs to market, the agency adopted in the early 1990s a new regime under which drugs might receive "accelerated approval." The new regulations, colloquially referred to as "Subpart H," were devised to expedite the approval of drugs intended to treat "serious or life-threatening illnesses," where such drugs imposed a greater than normal acceptable risk to the patient. That is, Subpart H was designed in part as an alternative means of approval for useful drugs that would otherwise fail the traditional risk/benefit calculus required for FDA approval. Subpart H facilitated approval of such risky (but apparently useful) drugs by imposing additional postmarketing restrictions above and beyond what was required through the normal mechanisms of approval.[6] In this way, the FDA was able to add another factor in favor of approval to the risk/benefit calculus. As the FDA explained in its Final Rule adopting Subpart H: "For drugs approved under the accelerated procedure regulations, the risk/benefit assessment is dependent upon the likelihood that . . . postmarketing restrictions will enable safe use."[7] In other words, the postmarketing restrictions "aim to enhance the safety of a drug whose risks would outweigh its benefits in the absence of restriction."[8]

In short, the FDA offered drug companies an option for accelerated approval the cost of which was submission to additional restrictions. Such restrictions take a variety of forms, including: restrictions on distribution of the product to a limited category of prescribers and the imposition of conditions of distribution on the performance of certain specified medical procedures.[9] Most important for present purposes, Subpart H provided for a truncated and expedited withdrawal process.[10] Under the relevant withdrawal provisions, the FDA can (following notice and an opportunity for a hearing) withdraw approval for any of the following reasons: (1) A postmarketing clinical study fails to verify clinical benefit; (2) The applicant fails to perform the required postmarketing study with due diligence; (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) The applicant fails to adhere to the postmarketing restrictions agreed upon; (5) The promotional materials are false or misleading; or (6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.[11]

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[5] *See* Noah, *supra.*, n 1

[6] *See* 21 CFR 314.520. *See also*, 57 FR 58942 (explaining that Subpart H applied to those circumstances where "FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted.").

[7] 57 FR 58942, 58955.

[8] *Id.* at 58952.

[9] 21 CFR 314.520.

[10] 21 CFR 314.530.

[11] *Id.*

Given the central importance of the postmarketing restrictions possible under Subpart H, it is not surprising that the failure to comply with such restrictions, or a showing that such restrictions are inadequate to assure safe use of the drug, result in an expedited withdrawal of the drug's original approval. As the FDA noted in its Final Rule, "If . . . restrictions do not lead to safe use, the risk/benefit assessment for these drugs changes significantly. FDA believes that if that occurs, rapid withdrawal of approval as set forth in this rule is important to the public health."[12]

It is not difficult to see the implications of Subpart H for the case of mifepristone. Danco Laboratories benefited from the accelerated approval regulations. The cost of such approval was a promise to comply with the postmarket restrictions the FDA thought appropriate under the circumstances. For example, if FDA were to conclude that Danco was not in compliance with these postmarket restrictions, or alternatively, that such restrictions were an insufficient hedge against the safety concerns associated with mifepristone, the agency would be well within its authority to commence withdrawal procedures. Indeed, it would be difficult to imagine that FDA would not regard it as its duty to do so, because in the absence of effective postmarket restrictions, mifepristone would presumably not be able to satisfy the statutory criteria for safety. If this were not so, mifepristone would have been approved under the traditional provisions rather than Subpart H.

Traditional Withdrawal Procedures

In the present case, if the FDA chose to eschew the truncated withdrawal provisions of Subpart H, it would still have recourse to the conventional mechanisms of withdrawal. In the Final Rule, the agency noted "that, in the event none of the grounds for withdrawal specifically listed in 314.530 . . . applies, but another ground for withdrawal under section 505 of the act . . . and implementing regulations at 21 CFR 314.150 . . . does apply, the agency will proceed to withdraw approval under traditional procedures."[13] Such traditional grounds include a finding (following notice and an opportunity for a hearing) that: (i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or (ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or (iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in § 314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or (iv) That the application or abbreviated application contains any untrue statement of a material fact; or (v) That the patent information prescribed by section 505(c) of the act was not submitted within 30 days after the receipt of written notice from FDA specifying the failure to submit such information.

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[12] 57 FR 58942, 58955.
[13] *Id. at* 58956.

Thus, if FDA concluded that any of the foregoing applied to mifepristone, it would be within its rights (and, I would argue, obliged) to commence withdrawal proceedings. It bears noting that while rare, it is permissible for the FDA to withdraw approval based on a re-evaluation of evidence previously considered. As the U.S. Court of Appeals for the Seventh Circuit noted in affirming the FDA's decision to withdraw an NDA less than one year following approval, "an interpretation of the [FDA enabling] statute prohibiting such new application of existing information would do violence to the paramount interest in protecting the public from unsafe drugs. The fact that the re-evaluation may have been inspired by a change in administrative policy is irrelevant."[14]

Imminent Hazard Authority.

In announcing the adoption of Subpart H as a Final Rule, the FDA observed that it considered the expedited withdrawal procedures therein to be appropriate for those circumstances in which there was no "significant hazard requiring immediate withdrawal" because the relevant pre-withdrawal hearing requirements balanced the need for "prompt action" with the need for "discussion and debate before withdrawal."[15] In circumstances involving an "imminent hazard to the public health," the FDA noted, "the Secretary of Health and Human Services may suspend approval of an application and then afford the applicant an opportunity for an expedited hearing."[16] This authority, vested solely in the Secretary of HHS (i.e., it is nondelegable), is perhaps the most dramatic mechanism that could potentially be wielded against mifepristone.

Given its sweep and force, it is a little surprising that "imminence" is not defined narrowly. The seminal case in this domain held that "imminence" is "not to be restricted to a concept of crisis."[17] The term is defined and the criteria to be considered are set forth in 21 CFR 2.5:

> (a) Within the meaning of the Federal Food, Drug, and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists.
>
> (b) In exercising his judgment on whether an imminent hazard exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.

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[14] *Bell v. Goddard*, 366 F.2d 177, 178-181 (7th Cir. 1966) (cited in Noah, *supra*., n. 1).

[15] 57 CFR 58956.

[16] *Id.*

[17] *Forsham v. Califano*, 442 F. Supp. 203 (D. D.C. 1977)(this case appears to be the only instance in which the "imminent hazard" authority of the HHS Secretary has invoked).

As with all of the aforementioned mechanisms for withdrawal, the Secretary's "imminent hazard" authority is ultimately subject to judicial review. But, as with the aforementioned means of withdrawal discussed above, courts are enormously deferential to the Secretary's conclusions in this context. As the court in *Forsham* made clear, to reverse the Secretary's decision, the challenging party must demonstrate "a substantial likelihood that the decision was a clear error of judgment and that [the Secretary] failed to articulate any rational connection between the facts submitted to him and the choice he made."[18] The District Court will only reverse the decision if it finds that the decision in question was "arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with the law."[19] This is an enormously high burden for the challenging party to sustain. It is made more difficult by the court's further holding that the challenging party will not prevail merely by demonstrating that there is a difference of opinion among "respectable scientific authority" on the question of whether the hazard can be properly characterized as "imminent." [20] Nor can the challenging party prevail by noting that the evidence relied upon by the Secretary "had [previously] been available for some length of time."[21]

Turning to the present case, if the Secretary of Health and Human Services were convinced that mifepristone presented a serious risk to public health, he or she could invoke this rarely used provision to immediately suspend its approval. If *Forsham* is a reliable guide, it is likely that such a decision would receive maximal deference from the courts (provided the decision was rooted in persuasive evidentiary support).

Conclusion

The aim of this statement was to provide a descriptive overview of the legal apparatus available to the FDA (and the Secretary of HHS), in the event that they were to conclude that mifepristone presents a threat to public safety, *or* if the postmarket restrictions that were fundamental prerequisites to its initial approval (under Subpart H) are being flouted or do not serve their intended purpose. As I noted at the outset, I am not currently in a position to draw such conclusions about mifepristone. However, if I were advising the FDA on how it should proceed, I would urge the relevant officials to diligently pursue answers to the questions relating to the safety of mifepristone, as well as those relating to compliance with or efficacy of the postmarket restrictions imposed on Danco under Subpart H. Fidelity to its central mission, namely, to secure the public's safety from dangerous drugs, requires nothing less.

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[18] *Id.*
[19] *Id.*
[20] *Id.*
[21] *Id.*

Mr. SOUDER. I would like to start with a question for Dr. Wood and Dr. Rarick. In your testimony, you pretty aggressively said, both of you, that there was no evidence to support the hypothesis that Mifeprex interferes with the immune response. NIH researcher Esther Sternberg's studies directly conflict with your assertion. Dr. Sternberg has conducted animal studies that demonstrate that RU–486 can suppress natural immune response. Dr. James McGregor of Los Angeles Women's and Children's Hospital has published work hypothesizing the pathway by which C. Sordellii causes multi-organ infection after suppressing the immune response. Ralph Miech of Brown University describes a mechanism whereby RU–486 suppresses the immune system and causes shock.

Have either of you read in entirety any of these papers, not just a summary, but have read those papers, and are you aware of any research that calls into question Sternberg, McGregor, and Miech's conclusion that Mifepristone may interfere with the immune response? You made a flat assertion. What about those studies?

Ms. WOOD. I will say, no, I have not read those studies in full. However, I spoke to Dr. Sternberg and discussed her findings and I would agree with you that there are certain—this is certainly a pathway that needs to be investigated. I think the issues and the use of the questions that arise about studies is that they are not questioning the studies themselves or even the outcomes of their studies, but they are, in fact, limited to particular species of rat and mouse and do not apply across even the different species of rats and mice. There is great variability in the level of the responses to different things.

This is an extraordinarily complex issue of how the immune system is regulated, either regulated up or regulated down by various——

Mr. SOUDER. So let me ask you——

Ms. WOOD. This is complex, and I agree with you, there are——

Mr. SOUDER. Let me ask you this question. So I don't misrepresent what you said, you said you have talked to Dr. Sternberg and you think that it is inconclusive, but in fact, in certain types of animals, the study shows that it suppresses?

Ms. WOOD. In her animal studies, it shows what it shows——

Mr. SOUDER. And——

Ms. WOOD [continuing]. But it is very preliminary——

Mr. SOUDER [continuing]. You are not familiar with McGregor or Miech's studies?

Ms. WOOD. I have——

Mr. SOUDER. Then how in the world under oath could you make an assertion like you did, under oath?

Ms. WOOD. I asserted that this is a very worthwhile and serious pathway to explore——

Mr. SOUDER. You said there was no evidence.

Ms. WOOD [continuing]. But it does not look like——

Mr. SOUDER. Under oath, you said there was no evidence.

Ms. WOOD. I did not say that.

Mr. SOUDER. OK.

Ms. WOOD. I said there is not compelling evidence.

Mr. SOUDER. Dr. Rarick——

Ms. WOOD. I said there needs to be further research.

Mr. SOUDER. Dr. Rarick, are you familiar with these studies? Have you read them through and——

Dr. RARICK. No, and I did not attend the meeting at the CDC. I similarly looked at some of the slides from the CDC presentation. I think the last part of your question was the most key word, which you said, don't you agree that they may be—that there may be a mechanism. I don't think we are disputing that there may be some mechanism of Mifepristone on glucocorticoid receptor issues and that the science in animals may have both sides of this story. Pregnancy, as you well know, is a complicated hormonal milieu with all kinds of receptor activations and inactivations of the various hormones that are happening during a pregnancy and pregnancy.

I think the last part of your question, which was "may," do we know that Mifepristone is causing an immune reaction in women? No. Might they? Possibly.

Mr. SOUDER. Well, it is very important because I was subjected to opening statement after opening statement with the implication that we are inserting politics. You in your statement said—it is really interesting, because if you want to restore the faith of the American people, they have to feel that there is actually an honest debate going on, and there is an increasing feeling that certain people who get control of the establishment research want to jam their views down everybody else and not listen to alternative research. And the assertion was made that there is no contradiction. There is a debate going on. We need to make sure that debate goes through.

Now, I was blown off in a question, quite frankly, to the Assistant Commissioner on the blood question. Dr. Harrison, my understanding of what you—did you go through the different cases on those who were reported? You seem to imply that these were transfusion cases and fairly serious bleeding, whereas I got the impression, oh, bleeding is common. This wasn't extraordinary bleeding.

Dr. HARRISON. I have had a chance, an opportunity to review 850 of the 950 cases, which we obtained by Freedom of Information Act. Of those 950 cases, I reviewed 68 women who were transfused. Of those 68 women who were transfused, we have 9 transfusion cases where the women received over four units of blood. We have 10 cases where they received over three units of blood and 38 cases where two units of blood were transfused. And there were also 10 cases where the adverse event report to the FDA did not document the number of cases transfused, and this is in settings where the clinical picture in the adverse event report was consistent with massive hemorrhage, which to me is unconscionable if you are actively trying to give the description of how much bleeding is there, to not even have a hemoglobin concentration or not even have an amount of blood transfused.

In addition to those that I reported in my paper, which is what I just quoted, there were an additional 12 in the adverse event cases from September 2004 to July 2005, and I would refer you to my spreadsheets that I gave you. And of those cases, the 12 that I mentioned were life-threatening hemorrhages. So of the life-threatening hemorrhages, it is basically 54 life-threatening hemorrhages altogether as of July 2005.

When I use the CTCIE criteria for coding these, that is a criteria that is used by the—developed by the National Cancer Institute to grade adverse events and to determine how serious they are so that you can compare them. What I used was a criteria of a women with a documented hemoglobin of less than 7—remember, the normal hemoglobin is 13—and transfused at least two units. So these are women who have lost over half of their blood volume.

I have in that time, from September 2000 to July 2005, 54 cases. Now, if you look at that compared to the number that the FDA reports, which is 119, that is almost half of the women who were transfused were in life-threatening situations. That is not the kind of bleeding that you normally expect from surgical abortion. It is also not the kind of bleeding that you normally expect from a spontaneous abortion. In fact, it is more comparable to the kind of bleeding you see in major motor vehicle accidents. So this bleeding that is being said as normal and expected is a large amount of blood.

Mr. SOUDER. Thank you, and one question for Mr. Snead. Is there a way that during additional research, and maybe Dr. Rarick or Dr. Wood would be able to answer, under normal research, that a drug cannot be taken—to me, taken off the market implies it is not coming back on, but could be suspended while additional research is done?

Mr. SNEAD. Sure. I take up three mechanisms in my testimony, two of which are mechanisms that require notice and an opportunity for a hearing before the actual approval is withdrawn. But the third option that I take up is actually an option that is exercisable only by the Secretary of Health and Human Services. It is a non-delegatable authority vested in the Secretary of Health and Human Services to declare a particular an imminent hazard. If he does so, the effect of that is to immediately suspend the approval of the drug and then the manufacturer then provided an expedited sort of post facto hearing to make their case for why it was improvidently declared an imminent hazard.

Mr. SOUDER. What about if—that still puts the burden on—because this is obviously a very explosive political question because it is abortion. Whether I like it or not or whether anybody likes it or not, it is a legal process and we don't have a right to stop it. I personally have my views on RU–486. Other members have their views on RU–486. The question is to say that it is being stopped and then the manufacturer has to make a case is different than saying additional research needs to be done, because that would imply that the government has determined that it is unsafe as opposed to additional research needs to be done.

Mr. SNEAD. That is right. In order to effect the imminent hazard privilege the Secretary enjoys, he would have to make a determination that it does, in fact, present an imminent threat, which is a judgment about the safety of the drug itself. There is a provision in the regulations for an administrative stay. The Secretary or the Commissioner has the authority to stay the effective date of any decision at any point in the process, which I think is more of what you are talking about, which is sort of—it is the equivalent in civil litigation to a temporary restraining order or a permanent injunction which sort of holds in place—which freezes the status quo and then tries to resolve whatever dispute or questions that there might be.

Mr. SOUDER. Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman.

Dr. Wood, I want to go back for a moment. I have always been one to—I don't like to leave things hanging. It seems like you were trying to say something and I want to give you an opportunity. The chairman asked you some questions and implied that you said something that you said you didn't say. I just wanted to give you the opportunity to clear that up if you would like. If you don't want to, that is fine.

Ms. WOOD. I would just make the point that I actually agree with the chairman and also with Mr. Patterson about the need for answering all of these questions. Is the immune system involved or compromised? What is it that causes this bacteria to become so virulent in women? What is it about pregnancy, either the ending of pregnancy either through termination or through childbirth, that has led to these deaths and these infections?

So I actually would agree that more research is necessary and my statement in my written statement and I believe orally was that I just don't—my reading of it at the point is that the evidence is not compelling to be conclusive that is the answer, but I certainly would urge any and all research to address these questions.

Mr. CUMMINGS. Thank you very much. Let me just go on from there. Tell me, Dr. Wood, could you explain why some women would prefer Mifeprex over a surgical abortion?

Ms. WOOD. Mifeprex is available to women much earlier in the course of pregnancies and so the termination of the pregnancy can be done in a matter of days after the pregnancy is established, of implantation in the womb, and up to several weeks. This is much earlier than a regular surgical abortion, which is required to wait a few more weeks. So this provides an earlier option if the women is determined to end pregnancy. It is also one that can be more private and also avoid surgery, which certainly many people prefer in making a decision.

I would also agree that access to all information about any known risks as they become known for any type of medical procedure needs to be available to women, and in the case of Mifeprex, because of the patient information that is required under the distribution restrictions on Mifeprex, that, in fact, we can work to assure that all women do get up-to-date information on any risk of any medical abortion.

Mr. CUMMINGS. It seems that as I listen to Mr. Snead and I am listening to your testimony and others, it seems as if the key question is where is the line drawn with regard to taking a drug off the market and I am just trying to figure out, what is taken into account when determining whether a drug should stay on the market, like this, for example? It seems that Mr. Snead has very eloquently stated all the options that could happen if the line is crossed. The question, it seems to me, is where is the line and when is it crossed.

Ms. WOOD. That question is the type of question that FDA has to deal with every day looking at every product when they get in a report of adverse events or deaths. And it is not simply the report of the deaths, but it is whether or not there are causal links, the magnitude of the response, how many people are affected in terms of the baseline use. There are many factors in trying to determine when a product should come off the market. It is not a simple question, but it is that balance of risks and benefits, and that is something the scientists and clinicians at FDA do every day and I would just urge that they be allowed to continue what they are doing, which is investigating this, evaluating it, and making their determinations without intervention.

Mr. CUMMINGS. Now, have you ever been in a position, you or Dr. Rarick, where you are, say for example, any position and certain evidence was presented to you and you were the person who suggested that we, or had the power to suggest that FDA take another look at a drug to determine whether or not it stays on the market at all, either one of you?

Dr. RARICK. I think I can speak to that, thank you. FDA does that kind of determination all the time. Every time you see a new labeling come out on a product, that means the FDA has relooked at the studies as well as the post-marketing events to assess it. Maybe there is a new safety issue that needs to be put on the label or not. When those discussions happen, there is always the option of considering withdrawal of the product if those risks outweigh benefits and that calculation is done often for all the products that are available.

Mr. CUMMINGS. I see my time is up, but just one last question. You heard Dr. Harrison.

Dr. RARICK. Yes.

Mr. CUMMINGS. Is there anything that she said that would make you all say, well, you know, maybe—I am just trying to be fair here—make you all say, well, maybe this is something we need to take another look at? I am just curious. Have you heard something, anything here today that causes you any kind of radar to go up?

Dr. RARICK. My perspective is what I have heard here today is extremely important, but it is all information that the FDA is well aware of.

Mr. CUMMINGS. OK.

Dr. RARICK. The adverse event reporting that Dr. Harrison is quoting is from the FDA.

Mr. CUMMINGS. OK.

Dr. RARICK. They are looking at this every day. They were involved in the CDC meeting last week. My impression from this discussion is that, yes, FDA is on the case. It is looking into this. These are really important questions and they should take an action that is appropriate with the data.

Mr. CUMMINGS. Thank you very much.

Mr. SOUDER. I want to make sure in the record that we are clear. Dr. Wood stated, this is a question to be studied, and to the degree I said there was—you said there was no evidence, that was incorrect. But you did say, if the immune system were suppressed, we would expect to see, and we didn't. We would expect to have seen this, and we didn't. Somewhere, we would expect to see this, and we didn't. Thus far, this pattern has not emerged. Basically, what you said was there was no evidence, and what I asked you was about three studies. Then you said those studies need to be studied further.

And then on top of that, you had denied, in effect, what was the consensus of the CDC panel, that there was, in fact, evidence. Dr. Rarick said in her statement, to date, there is no evidence that has emerged to support the hypothesis, which did not refute either of the three studies or the fact that the scientific community at a recent panel of which neither of you were present concluded the opposite conclusion.

Now, more research needs to be done on it, I will grant that, and I think that has been clear today. But it was not a false assertion that I made about Dr. Rarick said specifically in her testimony, no evidence, and Dr. Wood basically didn't cite any evidence. But I think we all agree more study needs to be done to see how common and how you disaggregate the two types of things.

Mr. CUMMINGS. Would the gentleman yield just for 1 second for a clarification?

Mr. SOUDER. Yes.

Mr. CUMMINGS. Mr. Chairman, all I was trying to do when I asked the question is I don't like for witnesses—I think when people are—these are professional people and I don't want them to ever be in the position where they come before the committee and for whatever reason they don't get a chance to explain something that puts into question what they have said, their credibility. I just think it is, as one human being to another, bad to do that. That is all.

Mr. SOUDER. And I understand the gentleman's concern, but you also know in a 5-minute rule that she had answered the question and she was then off to another. I didn't mean to cutoff her ability to respond, and that is why I want to grant that you, in fact, said more study was needed and the direct "there was no evidence" quote was actually Dr. Rarick's, not Dr. Wood's, but Dr. Wood had a series of things that suggested it wasn't. I want to make sure the record reflects accurately, as you did.

Mrs. Schmidt.

Mrs. SCHMIDT. Thank you, Mr. Chairman. I actually have questions for Dr. Rarick, Dr. Harrison, and Mr. Patterson, if that is all right.

Dr. Rarick, Dr. Wood stated that politics—she didn't want to see politics triumphing science once again, and none of us want to see that. My concern is how this product came to market in 2000. Dr. Wood stated that controlled trials were performed in support of the RU–486 FDA application. Could you tell us what the control group was in those trials that made those trials controlled? More specifically, was there a double-blind study, and if so, how did it result?

Dr. RARICK. Certainly. In this area of pregnancy-related conditions, including contraception or birth control, oftentimes the FDA accepts clinical trial designs that are appropriate and use historical controls. So, for example, you can't have women who come in and want to contracept and suggest that they should be blinded and randomized to placebo versus a contraceptive that you expect to work and expect that to be an ethical trial design.

Similarly, in medical abortion, when a woman comes in with a request to terminate a pregnancy, you can't suggest to her, well, we think this pill will terminate your pregnancy based on all the science, but we want you to sign a consent form that states you will be randomized to a pill that we know has no effect—a sugar pill, a placebo pill—on your pregnancy and then let us know if you abort or not. That is just simply not a reasonable trial design.

In this setting, you know if you don't do anything, there is almost a 100 percent chance that they will continue to be pregnant, although there is a miscarriage rate, as you well know. But in an early intrauterine pregnancy termination, you can't expect placebo to have any potential effect. So you go back to the sort of historical control concept, that if you didn't give the woman anything, what would be the chances of her aborting versus giving her something.

Mrs. SCHMIDT. Mr. Chairman, I have to comment on this because I am troubled by this statement. In 1995, my father was involved in a very critical car wreck and he almost died and they put him on a clinical trial regarding getting him off of oxygen, because the longer you stay on oxygen the harder it is to get off the oxygen. It was a double-blind study. We didn't know whether they were giving him the opportunity to wean off quicker or not. The alternative obviously is more of an opportunity to die.

So the argument that a double-blind study can't be used in this case but it can be used in a life or death case of a man in an ICU unit at University Hospital, that just doesn't fly in my face and that is what makes me concerned with all of this, is that I believe politics was there in 2000. I think that while I was back home in another role in my life, I think that there was a rush to judgment to get this drug to market and what we are seeing now are some problems that are arising from it.

My concern is we don't have adequate knowledge one way or another whether RU–486 has a direct or an indirect cause for death. We do know that there is a relationship between the death and the taking of the drug. We don't know whether it is direct or indirect. But we do know that there is a relationship. And my concern is that politics, once again, is playing out.

But my next question is actually for Dr. Harrison. Your colleagues say that if the theory were true that Mifeprex comprised the immune system, then we would see a higher rate of other kinds of infections. Your colleagues say this. What is your response to that?

Dr. HARRISON. Well, I think the focus of the CDC meeting and most of our discussion today has been on the infectious deaths, but there were actually at least 7 other life-threatening infections to date in the 850 severe adverse event reports that I reviewed, 1 of them being a 15-year-old who spent several weeks in the intensive care unit but lived.

So there is an issue of critically looking at those infection-related complications and there is a secondary issue in even identifying those infection-related complications, because if Mifepristone suppresses the immune system, the infection may not be pelvic, and if it is not pelvic, it may not be recognized as being related to the Mifepristone abortion and, therefore, never reported. So we have a number of women walking around potentially with a decreased immune system or decreased ability to fight off infection whose connection with their Mifepristone abortion will not be known, and that is a big concern.

Mrs. SCHMIDT. Thank you, and my final question is for you, Mr. Patterson. I am so glad that you are brave enough to bring this to our attention and I know that your daughter is smiling down on you. You are a very brave person.

What do you have to say about the assertion that the benefits for RU–486 weigh the risks associated with it and what do you think should be done to protect other families from the same tragic fate that your family continues to experience?

Mr. PATTERSON. I think if you were to ask Holly here today, had she lived, if the benefit outweighed the risk, I think she would disagree. I have spent many, many hours researching this drug and I can tell you that I feel very strongly about the link that this drug does impair the innate immune system and predisposes women to these—and can predispose these women to serious and lethal infections. There has been a lot of discussion of that at the CDC, FDA, and NIH conference.

I think the research is absolutely necessary. I think we have information that has come out from very well renown and respected doctors. It is very compelling that we need to pursue this research to answer these questions.

Had Holly been given all the information in the very beginning, you know, talking about the risk-benefit profile and weighing those options, I think that had she been given all the information she needed, she certainly would not have chosen an RU–486 abortion because Holly was not the kind of young lady that would risk her life for any reason whatsoever. Being the pinnacle of fitness and the type of healthy individual that she was, she would have chosen an alternate method and I can't say enough that it is all about having all the information to make an informed choice that is in the best interest of that particular individual and the family that are making those decisions.

Mr. SOUDER. Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman.

I am trying to sort out these different positions and I guess the first thing we are talking about is an infection that has proved to be fatal in some cases and this infection is called C. Sordellii. The first question is, is this infection caused by this drug? People who didn't use this drug have had this infection, is that accurate, Dr. Rarick?

Dr. RARICK. Yes.

Mr. WAXMAN. So it is not related exclusively to this drug. Now, we know that some people who used this drug had the infection. We don't know whether it caused the infection, is that accurate?

Dr. RARICK. Correct.

Mr. WAXMAN. So we need to get an answer to that. If the theory is that the immune system is suppressed because of the RU–486, wouldn't we have a lot of evidence more of other infections besides this one, because this is a fairly rare kind of infection, isn't it?

Dr. RARICK. It is a very rare infection and I think this situation is that it seems to be cropping up in pregnancy-related events, not just medical abortion, but deliveries, vaginal and Caesarian, and other conditions of post-pregnancy conditions. I think the FDA is actively looking at whether they agree or not that Mifepristone has any component of making it a higher risk in women who are using it for medical abortion versus other kinds of miscarriages or pregnancy termination.

Mr. WAXMAN. Well, this is not an issue that Congressmen should decide. This is a very clear scientific issue. Evidence ought to be reviewed very carefully. The Food and Drug Administration, the Centers for Disease Control, the National Institutes of Health all met on this issue this last week, is that correct, Dr. Wood?

Ms. WOOD. Yes.

Mr. WAXMAN. So they are looking at it. Dr. Harrison, do you have any information that the FDA does not have?

Dr. HARRISON. No. I have less information than the FDA does. My information on the adverse event reports were obtained by FOIA——

Mr. WAXMAN. From the FDA?

Dr. HARRISON [continuing]. From the FDA, and my information that I presented on the risk of C. Sordellii was directly from the notes that I took from the meeting in Atlanta on——

Mr. WAXMAN. Were you able to share——

Dr. HARRISON [continuing]. Dr. Fischer and Dr. McGregor's testimony, who both are from the CDC.

Mr. WAXMAN. Were you able to share your views with people at the FDA and perhaps at that meeting last week?

Dr. HARRISON. I was not a participant and the panelists, the speakers and those who were in research, were segregated from the rest of the observers. I was in an observer spot and not allowed to talk with the speakers until after.

Mr. WAXMAN. Are you able to submit your views to them in writing?

Dr. HARRISON. Someone from the FDA has requested a reprint of my adverse event analysis that was printed in January and I think that was the last request that I had or contact with the FDA.

Mr. WAXMAN. You are listed on our list of witnesses today as a member of the Mifeprex Subcommittee of the American Association of Prolife Obstetricians and Gynecologists. In January 2001, your organization issued a statement—this was several months after the FDA's approval of Mifepristone. The statement said, "The American Association of Prolife Obstetricians and Gynecologists opposes the destruction of an unborn human being at any stage of development. Therefore, we oppose pharmaceutical abortion with the same vigor that we oppose surgical abortion." Would your organization hold the same position on Mifepristone no matter what the safety data said?

Dr. HARRISON. I did not write that statement, although I am a member of the American Association of Prolife Obstetricians and Gynecologists. We characterize ourselves as pro-woman and prolife and this is a women's health issue. When it becomes clear that a method of abortion is 10 to 50 times more risky than its alternative, then this takes it out of the realm of the abortion debate and puts it into the realm of the women's health debate——

Mr. WAXMAN. No doubt about it, but your organization—excuse me, your organization——

Dr. HARRISON. I would like to finish, please.

Mr. WAXMAN. No, no, let me, because I only have a very limited time. Your organization's position is that you oppose destruction of an unborn human being at any stage of development, whether it is a pharmaceutical abortion or a surgical abortion. So if that is your organization's position, it is really unrelated to how safe or unsafe this may be. I gather what you are saying is in addition to that, you feel it is unsafe, but your organization started off with the position that you don't want any abortions under any circumstances. Do you subscribe to that view?

Dr. HARRISON. I wouldn't agree with the way you said it, no. What I would say is that in this particular——

Mr. SOUDER. Dr. Harrison.

Dr. HARRISON. Yes, sir?

Mr. SOUDER. You do not have to state your position on abortion or I am going to ask all the witnesses their position on abortion.

Mr. WAXMAN. Well, Mr. Chairman——

Mr. SOUDER. The question is what the——

Mr. WAXMAN. Mr. Chairman——

Mr. SOUDER [continuing]. Issue at hand is, not what her personal position on abortion is.

Mr. WAXMAN. Mr. Chairman, she is here representing an organization and that organization has taken a position against abortion under any circumstances. And they took that position when RU–486 was approved without any of these other complications or possible causations or connections ever came about. And so my question of her is since they took that position, no matter what the safety data said, how I should view that as a representative from that organization. Did you agree with the organization's position even if the safety data didn't convince you further that this is a possible problem with this drug?

Dr. HARRISON. If the issue were whether or not there is a human being being destroyed during the RU–486 abortion process, that is a separate and completely different issue than the issue this committee is authorized and mandated to look at, which is oversight of the FDA process by which this drug was approved, and are they doing their job to take an unsafe drug off the market.

Mr. WAXMAN. Well, I appreciate that. I appreciate that, and our job is to make sure that the FDA is doing its job. But FDA is a scientifically based organization. They have to follow the science. It may lead to a conclusion one way or it may lead to a conclusion another way, but I want them to follow the science, not some preconceived notion, and I think that is the important point that I would make.

I see my time is up and I will conclude on that note.

Dr. HARRISON. May I respond to that?

Mr. WAXMAN. Well, no, because we are not going to argue that issue. The position, it seems to me, is there may be a problem that is related to this drug. There may be a problem that has no relationship to this drug. Let us get the truth. Let us get to the scientific evidence and let the scientists decide it, not politicians, no matter what our views may be on the abortion question, because this is strictly, to me, a scientific question.

Thank you, Mr. Chairman.

Mr. SOUDER. Mr. Waxman and I fence a lot in the media, even though we have tremendous personal respect for each other and get along real well, and it is awkward when we have deeply held views of he believes that I and others are trying to impose our political views and I and others believe the political views have been imposed on the system already.

But what I really find disconcerting, and I understand where you were headed here, because there are two issues. We can't undo whatever abortion rights are in America. This is a question about this drug. But you cannot possibly hold the position that prolife people who oppose abortion can't participate in a debate——

Mr. WAXMAN. And I wouldn't take that position.

Mr. SOUDER. Then what——

Mr. WAXMAN. I certainly wouldn't take that position.

Mr. SOUDER. What is the relevance of her position on RU–486, because if you are asking her, can she be neutral on the research, that is the question, not what her position is.

Mr. WAXMAN. My question related to the fact that if she is representing an organization that took the position, we don't care about safety data, we are just against the drug accomplishing the purpose for which it is intended, which was to terminate a pregnancy, if that is your position—let us put it the other way. If you had somebody who said, I want to terminate all pregnancies whether anybody wants to do it, which is not my position, by the way. I don't want to see abortions, but I don't want the decision made by you or Mr. Cummings or myself. It ought to be made by the individual with the consultation with a physician and an ethicist and others. It is a personal decision, not one to be decided in Washington.

But if somebody takes the position that they are from an organization that is against RU–486 under any circumstances, even if it were safe, then you sort of wonder, well, if they come in and say, well, we don't want this drug because it is unsafe, I think their views ought to be submitted to the FDA and they ought to evaluate them.

Mr. SOUDER. I don't think that is a—I think that, in effect, that is why so many conservatives have a deep distrust of our current research structure when we hear that it is nonpolitical, because, in fact, what you just outlined was something—a position that somebody who deeply believes that all babies are human cannot detach that view or should be somehow demeaned if they belong to any organization that is pro-life as if we are under extra scrutiny as a doctor, as a researcher, as a politician, that somehow, then, we are not allowed to have a scientific discussion without wondering whether our motives are impure.

Mr. WAXMAN. Well, she is not here as a well-known doctor, as I understand it. She is listed as here representing that organization. Now, if she happened to be somebody from NIH or a researcher very well known in the field and she is here for her expertise alone, that is one thing. But she is here representing an organization.

Mr. SOUDER. It is really interesting, because she gave very compelling testimony, very detailed testimony on the individual cases, more than we got by far on blood transfusion actually from FDA, and that rather than debate about her testimony, you choose to attack the witness.

Mr. WAXMAN. No, I am not attacking her, but Mr. Patterson's daughter didn't die from hemorrhaging. She died from this particular infection and this infection is a very dangerous infection and we need to know if it is connected to this drug. If it is, even though I am pro-choice, I would be the first, along with you, to say it ought to be taken off the market, or it ought to be labeled as such. But if it is not a safety threat, then I don't think it ought to be accused of being a problem just because it shouldn't have been approved in the first place by the people who want to take it off the market.

Mr. SOUDER. Furthermore, she is a published author in research documents. I——

Mrs. SCHMIDT. Mr. Chairman, I think in fairness, I want to know where everybody stands on the issue of abortion——

Mr. SOUDER. I don't think——

Mr. WAXMAN. Do you want to start off with yourself?

Mrs. SCHMIDT. Sure. I would be more than happy to.

Mr. SOUDER. Reclaiming, I think the line of questioning was inappropriate. I made my statement. Mr. Waxman is the senior ranking member of the full committee. He is free to do that. I think the public can judge whether that was a fair approach, but it certainly will reinforce people across the country who are watching, a feeling that there is a discrimination against people who are pro-life from being able to participate in research, and that is some of why there is so much questioning about this whole science debate.

Mr. WAXMAN. Would you yield to me just for me to make one comment? I appreciate your views. I don't agree with you. But the only comment I would make is that the Government Accountability Office did an evaluation of FDA's action on the Plan B contraceptive drug, and even though the scientific committee appointed to review it said it should be approved, even though the researchers at NIH said it should be approved, it appeared that a political judgment was made because of the Bush administration that it shouldn't be approved and its approval is now in limbo. Many of us look at that as clear politics when the science points in a different direction.

I want to know what the science says about this issue. You say it is compelling. It is not compelling if scientists are still evaluating the matter. I want them to see whether it is compelling, whether there is a clear case made, and I don't want politics interfering with science.

Mr. SOUDER. You can keep repeating that, but the funny thing is, I have been a staffer here, I have been a member here. We all know who requested the GAO study, who has picked on the GAO study, which is heavily steered. GAO will do a study on either side depending on who basically pushes it and what mixes are. We have gone into this.

Mr. WAXMAN. Well, now you are attacking the GAO's credibility just because it came up with a study that you disagreed with.

Mr. SOUDER. No, I am questioning——

Mr. WAXMAN. That is more of an attack than I ever did with Dr. Harrison.

Mr. SOUDER. As the GAO——

Mr. WAXMAN. And I didn't mean—I attacked the research——

Mr. SOUDER. As I have said, when you get into controversial political subjects, the GAO, how you phrase the question, who does it, in any honest—forget here for a second that the TV is on—you know full well that we have problems in the GAO as far as what kind of study you get back, and to act like it is a pure scientific study out of the GAO—they do good research, they research it, but they are going to have a bias based on who is put on a given study and who is requesting the different study. And if I request it with Republicans, you are going to get a slightly different study back than you do.

There are subjects where they aren't that kind of laden with the political overlay on this and the GAO will be very forthright. You can go through the researchers they contracted. You can look at the footnotes. You can look at the previously published records of it. I am saying the GAO is transparent on it, but when you go through the evaluation, you will see who they hired as a contractor will determine what research they get back.

Mr. WAXMAN. We have another Member who wants to ask questions——

Mr. SOUDER. Yes, I——

Mr. WAXMAN [continuing]. But I just want to defend GAO. Requesting a study by GAO doesn't mean that they have to come out with your preferred conclusion. I think they have a lot more integrity and honesty than you are suggesting. They can decide who they are going to do the investigation. I think they are a reputable source of information. Sometimes they come up with conclusions I like, sometimes not, but they come up with the facts and then we can draw the conclusions. I want the science reviewed and then we can let the appropriate policymakers reach the conclusion, but——

Mr. SOUDER. Ms. Watson——

Mr. WAXMAN [continuing]. Ms. Watson has been very nice here.

Ms. WATSON. I came in late and I am sorry about that. I would like to know what we are investigating and looking at in this particular meeting. Now, reading from the information that was given to us, it says "RU–486: Demonstrating a Low Standard for Women's Health?" May I ask, I would maybe ask Dr. Rarick or Dr. Harrison, the question. Let me start with Dr. Rarick.

Are we talking about a low standard for women's health, and if so, what is that? And are you agreeing that we have seen more women die after using this drug than women who die after having abortions? I just want to focus this discussion. I think we have gotten off the track. So can you respond to that, because we are looking at a low standard for women's health. At least, that is what I thought this meeting was about and not our beliefs and what sides we are taking. So can you answer that question, the low standard question?

Dr. RARICK. Certainly. I will start with that. Mifepristone in its review at the FDA was held to the highest standards, similar to any drug product that is reviewed in the Center for Drugs. It was reviewed in a rigorous way. It took over 4 years from its submission to its approval. It was appropriately labeled. It was held to the highest standards for women's or men's health at the FDA and I believe they are still treating it that way. They are looking at the issues that you are asking about.

Are there more deaths reported with Mifepristone than with surgical abortion? Some would say that there is tenfold more deaths. I think we just heard that reported. But again, we have to think about how they are looking at this data. Is there a way to get more accurate data on surgical abortions, etc.? Is there a way to understand the Mifepristone-associated deaths so that they can be prevented? The issue is risk and benefit. They are looking at that very seriously and I think it is being held to the appropriate and high standards.

Ms. WATSON. As the department of government that looks at drugs and their usage and results, what would be the next step if you then conclude that there appears to be a higher number of deaths associated with the approval and the use of this particular drug? What is the next step?

Dr. RARICK. Well, the next steps would be to look into those types of deaths in all pregnancy-related events to try to understand those better, make providers aware of those infections and that potential, understand how to prevent it, understand how to treat it, do women the service of understanding pregnancy-related deaths in the broader sense, not just related to Mifepristone. Many more women die from childbirth than die from using Mifepristone for medical abortion. Putting money into those questions, surveillance into maternal mortality, appropriate money to explore maternal mortality in its broadest sense, those would be the next steps.

Should the FDA look at all this information? Absolutely. As was said before, they have all the information and more than Dr. Harrison has referred to. They are looking at it very seriously. If they believe that—they come to the conclusion that the risks do not outweigh the benefits, they will take appropriate action.

Ms. WATSON. OK. And do you feel that we are demonstrating a lower standard for women's health?

Dr. RARICK. Not at all.

Ms. WATSON. All right. I would hope that this committee would provide the oversight as FDA moves along and we would then look at the empirical evidence that would emanate from your studies to address this question. If we are demonstrating a lower standard, then provide the scientific evidence. I would beg that we don't discuss the "A" word in terms of looking at this particular drug. It gets us off track, as it did just about a minute ago. What I want to be presented with as a decisionmaker is what evidence we might have that we have approved a drug that lowers the standards for women. Thank you.

Mr. WAXMAN. Will the gentlelady yield to me?

Ms. WATSON. Yes, I will, certainly.

Mr. WAXMAN. I wasn't even aware of it until you just pointed it out. The chairman said it depends on how you ask the question, but the hearing is titled for today, "RU–486: Demonstrating a Low Standard for Women's Health?" so that is the way we are asking the question. I think we need to see whether there is a—and you answered that question and I was pleased with your answer, but I think the question should be, is there a connection between Mr. Patterson's daughter and the five people that have died from this particular infection and the use of RU–486? That seems to me the key to it, because if there is a connection with the use of this drug and getting something as deadly as this infection, that is a serious matter. So we need to explore it, but evidently it is not so clear when we find people have had the infection who didn't have the drug. So I agree with you. Let us get the science. Let us get the facts.

Mr. SOUDER. Dr. Rarick, I was a little confused by your response. You said that if, in fact, there were deaths, you would work for or believe there should be further notification to doctors. I inserted this earlier, but Palladone, Purdue Pharma agreed to voluntarily suspend, and they said, to date, FDA is not aware of any patients who had life-threatening side effects from drinking alcohol while taking Palladone, but they took it off the market.

Tysabri Biogen voluntarily suspended marketing of the drug as well as its use in clinical trials until more detailed information could be gathered on one death and one other adverse effect.

In NeutroSpec, Palatin Technologies voluntarily suspended sales and marketing of NeutroSpec. No determination was made regarding the relationship between that and reported adverse effects.

In Cylert, Abbott chose to stop sales and marketing based on 13 reports of liver failure, but they did not grant—and RU–486 had 10 to 14 times more than surgical abortion, even though in this case liver failure was 10 to 25 greater in the general population.

Bextra, Pfizer voluntarily withdrew Bextra from the market even though it concluded that the overall risk versus benefit was unfavorable.

In Baycol, they withdrew after reports of 31 deaths. In Roplin, it was 5 deaths.

In Lontronex, it was a total of 70 cases of adverse effects of which 34 required hospitalization without surgery and it was pulled off.

In Orlaam, it was discontinued after a report of severe cardiac-related events among opiate-addicted patients. They pulled it off the market, not just warnings.

So is your position that FDA should treat this drug unlike other drugs, because when there are adverse effects with deaths and so on, at the very least, you think it would be suspended. That has been the whole pattern. The problem here is you have a drug company that only has one drug. It is in the Cayman Islands. There is no incentive to do what all these other companies did which went off the market. And so what is the responsibility of the Federal Government when the private sector won't act responsibly like the others.

Now, I happen to believe, even though I don't want RU–486 on the market, that there may be some debate here as to whether it is the primary, and that is why I was asking questions of can it be suspended while we find that out. But I see no pattern of FDA that we leave something on the market while we are doing that study, because it is clear that it was toxic in a disproportionate amount if you are using RU–486, that the blood transfusions were certainly disproportionate, and under any standard of the past, you would at least suspend, hence the question of the hearing.

Dr. RARICK. I would simply disagree with you. You can list all the ones that have been suspended, but you have to think of the thousands of drugs that are on the market that have post-marketing reports of deaths. The easiest example is Viagra, where we had at least several hundred deaths during its first year of prescription, the same company, Pfizer, that you mentioned there for Bextra. There are all kinds of examples of post-marketing death adverse event reports and other serious adverse event reports where the majority are certainly not suspended from marketing.

Mr. SOUDER. Even if it was directly related to that product, the FDA does—then what standard would you have FDA intervene?

Dr. RARICK. The standard that they use, which is a risk-benefit analysis for each particular case.

Mr. SOUDER. Mr. Snead, what is your response to that?

Mr. SNEAD. I think, essentially, that is exactly right, namely that you need a risk-benefit analysis that is undertaken to determine whether or not a drug is initially approved. But I would like to add something that I think would be informative to the Members. What we are talking about here as a legal matter is a drug that has been approved under Subpart H, and what that means is that creates an inference that the FDA in approving Mifepristone had a concern, safety concern, that required additional safeguards beyond the normal safeguards that attend a normal risk-benefit analysis.

In the passage that I read before from the FDA's final rule, they said the risk-benefit analysis that yields the conclusion that this should be approved assumes that these post-marketing requirements will, A) be effective, and B) be observed. So there has been much discussion about the safety piece of that particular question. But what seems to be getting lost among the discussion is there is a second question, a second grounds under Subpart H, which is a factual question about the compliance with the post-marketing restrictions by Danco Corp.

So I would just draw the committee's attention back to the fact that, of course, safety is a principal concern as laid out in the withdrawal approvals of Subpart H as well as with the other withdrawal approvals that I take up in my written testimony, but the question of compliance is equally important of a question, because without meaningful compliance by Danco, the risk-benefit analysis is not what the FDA intended it to be. The risk-benefit analysis depends on the assumption that there is compliance, and if there is no compliance, then the risk-benefit analysis is substantially different.

Mr. WAXMAN. Mr. Chairman, could you yield to me?

Mr. SOUDER. Yes.

Mr. WAXMAN. Do you have evidence of noncompliance?

Mr. SOUDER. I have no evidence of any kind. I am just simply describing to you what the considerations are.

Mr. WAXMAN. So you are saying if there hadn't been compliance with the limitations——

Mr. SOUDER [continuing]. I am making a conditional statement. If the FDA were to determine that there was no compliance, then they would have additional grounds to withdraw approval under Subpart H.

Mr. WAXMAN. But I hadn't heard anybody assert that there hadn't been compliance of the approval itself under the Subpart H. Of course, this is unusual, because most drugs are just approved and once they are approved, they can be used for any purpose. This one was approved for limited purposes under limited circumstances so that there would be extra care taken. I guess I should ask that question of Dr. Rarick. Am I correct in that? It wasn't——

Dr. RARICK. Correct——

Mr. WAXMAN [continuing]. Approved like most other drugs, go ahead and use it——

Dr. RARICK. There was a determination that it shouldn't be released through pharmacies, that it had to be provided by specific types of prescribers.

Mr. SOUDER. And I should say for the record that we did invite Danco so we could address that question and they withdraw 2 days before the hearing and we didn't have a chance to get somebody else to directly address the question, but it is a fair question.

Mr. WAXMAN. It is not a fair question unless you know there has been some non-compliance.

Mr. SOUDER. No, your question is a fair question, because we don't know for sure about compliance. I tried to address that with FDA. I don't think, personally, that what was tested has been followed through the way it was tested, but the Assistant Commissioner explained why she thought that was still allowable, but we don't have Danco here and we don't have a substitute for Danco to follow through that question, but it is a question we need to follow-up in our written questions and we said at the beginning that I was going to do that with Danco.

Dr. Harrison, could you talk about the proportionate use effect, too? Viagra is used over and over. RU–486 would not be. And any comments you had on Dr. Rarick saying, look, there are other drugs we allow on the market, because that is a fair point. If there are lots of drugs on the market that have adverse effects, why should this be treated differently than those?

Dr. HARRISON. The issue is not the absolute number of adverse events. The issue is, as is stated in the FDA letter to this committee, the evidence whether or not RU–486 was causally related to the adverse events, the timing of the event—remember that these RU–486 septic deaths happened within 7 days. There is no issue of confounding factors here. These women were healthy. They didn't have other medical conditions that could explain why they would suddenly get an extremely rare bacterial infection that doesn't usually kill normally immuno-competent people. How severe these events are—the death is the ultimate severe adverse event.

And I would have to add that transfusions are also a significant severe adverse event, and to minimize the significance of having a blood transfusion is to underestimate the care that goes into clinically judging whether or not this person needs a transfusion. Transfusions aren't done lightly. They are done when there is a significant risk to the person's life.

Can the adverse events be predicted or avoided? The CDC meeting was absolutely clear that at this point in time, there is no way to predict who is going to get—who is going to die from C. Sordellii.

Because we can't predict who and we can't identify risk factors, we also can't avoid C. Sordellii in Mifepristone abortions. There has been a consistent spontaneous—a consistent rate, excuse me, of about 1 death for every 100,000 Mifepristone uses. So if that continues unabated while we debate these questions of how much research and who gets the grant money and all that stuff, that means that for every 1,000 uses of Mifepristone, one more American woman is going to die, and I think that is something that has to be put into perspective. These are human beings that are being subjected to a completely unnecessary risk.

Surgical abortion is available and legal and safer, and how safe is the alternative treatment, and that is the other issue. Surgical abortion is available. It is legal. And to say that Mifepristone is being used in cases where surgical abortion isn't available, think about what would have happened to these transfusion deaths if there hadn't been surgical abortion available. Any place that has the capability to—excuse me. Any place that doesn't have the capability to have an abortion clinic also doesn't have the capability to do transfusion. We are talking pretty sophisticated medical facilities. So the person you absolutely do not want to use Mifepristone is the one who has no access to surgical facilities to complete this under an emergency circumstance, so I think that is kind of a spurious argument.

So that would be my response. Thanks.

Mr. CUMMINGS. Mr. Chairman, may I please——

Mr. SOUDER. Yes.

Mr. CUMMINGS. Thank you.

Mr. SOUDER. Mr. Cummings.

Mr. CUMMINGS. I have sat here and I have listened to all of this and I was sitting here saying to myself, I am so glad that there are women making these arguments. I would hate to see a group of men. They would probably say that we were not as sensitive as we need to be, and I say that to say this, that I think we are all concerned about women's health. As a matter of fact, I know that we are.

I don't think that in this country we are talking about low standards. Let us not kid ourselves. This is the United States of America. There is no way that I think any member of this panel would in any way accept a low standard or even a mediocre standard. The witnesses, I know you feel the same way. We may differ on your opinions and what have you.

The key is, Mr. Patterson, is we want to make sure that we do everything in our power, as I know you want us to do, to make sure this does not happen to anyone else. That is what this is all about.

And I would hope and I would think that you, Dr. Rarick, when I asked you the question a little earlier, because I really wanted to get a sense of exactly—obviously, there is a procedure that you have there at FDA, and obviously, and you can tell me if I am wrong, you try to keep the politics out of it because you are talking about people living and dying, I guess. I trust that you do.

But you have heard the testimony of Dr. Harrison and I would assume that you would be, as we all are, as sensitive to women's health. Is there anything that you have heard that you would question whether you all have a low standard? I know that may be a sort of self-serving question and I am not trying to do that, but I am trying to get to the bottom of this, because sometimes we can get so caught up in our politics that we forget where we are trying to get to and we get sort of off-track. The key is that we want to make sure, all of us, that FDA has a standard which will protect every woman with regard to her health choices.

So that leads me to this. Somebody said a few minutes ago, I think it was you, Mr. Patterson—it was you—when you were talking about your daughter, you said if there was information, if she had access to all the information, she probably would not have made that choice.

Now, I am asking you, based upon all that you know, Dr. Rarick, is there anything that you could have or the FDA could have put on the label or put on the little description of the drug's side effects, whatever, that should have been there, just based on what you know to this date? I am not talking about—I know there is still research to be done and all that kind of stuff—that should have been on there?

Dr. RARICK. Well, I would stand behind the FDA's labeling at each point when they revised their labeling, and if you look at the current labeling, it does describe that there has been some unusual and severe bacterial infections and deaths. It describes some of the way the regimen was given in those cases. It provides that information.

I agree with you that the FDA has to look at this very seriously and always decide, do the benefits remain to outweigh the risks?

If you ask me about high standards, I would say the FDA holds this to a very high standard. I believe if you are looking for low standards in women's health, it would be that we don't have very much information about maternal mortality in general, not just post-abortal or post-medical abortion mortality, but just infections and pregnancy outcomes, any events in general.

But in terms of Mifepristone being held to a particularly low standard, absolutely not. It is held to the highest standards. I think the FDA is considered the most rigorous regulatory body in the world and it, of course, meets those needs.

I agree with you that these things are incredibly serious. Nobody is trying to minimalize any of these events. I believe the FDA is looking at this from their scientific viewpoint. They at the meeting last week I think were quoted as saying they initially saw this as probably a simple drug-based association and they realized when they looked into it that simply wasn't true, that it was much more complicated than just Mifepristone and infection and they are looking at it.

Mr. CUMMINGS. Now, you said the labeling has changed. I am going to get back to you, Mr. Patterson, in 1 second. I see you shaking your head. But you said the labeling has changed, is that right?

Dr. RARICK. Yes. The labeling has been updated, I think at least three times since its original approval.

Mr. CUMMINGS. And I take it that when Mr. Patterson's daughter took the—there have been changes since Mr. Patterson's daughter used this medication?

Dr. RARICK. Yes.

Mr. CUMMINGS. Maybe one of you all could tell us, were those the changes that you just authorized? You said something. I am just trying to figure out, have we made much progress with regard to going back to what you said, Mr. Patterson, putting it out there, as much information as possible that we feel comfortable is accurate?

Mr. PATTERSON. Well, first of all, I would like to say again that if Holly had all the information to make an informed choice, she wouldn't have chosen Mifepristone or an RU–486 medical abortion.

There is evidence that a death did occur in Canada with an infection and she, in fact, did die from C. Sordellii, and that was what I uncovered in my medical research that was not very well known or very well published. As a matter of fact, the author of the paper of the woman who died in Canada was Dr. Christian Sinave. It just so happens that at the time, my wife and I, when we called Dr. Sinave, we were the very first person or concerned people to call about that particular infection as it is associated with RU–486. He said in his own words that he had been discouraged to write the paper and that we were like the only ones that had ever showed any interest, and since then, there has been a considerable interest over this infection and its relationship with the drug.

To say that this drug, there is no causal relationship, I think is ridiculous. My daughter took the drug and she died. I mean, it is that simple. So the medical community was aware of it. Danco was aware of it. The Population Council was aware of it and there were studies showing that there were infections as a result of medical abortion. However, Holly was not indicated in the label and Holly was not given that information.

Since my daughter died, I have been to Washington. I have discussed my concerns with the FDA over these safety and health concerns. There have been—consequently, there have been four more women died after Holly and some very shortly, within months, after Holly. As a matter of fact, with the reporting, it took one of the deaths right after Holly, it took almost a year and a half to get reported. That is why today I have discussed there needs to be some very accurate mechanisms to be able to evaluate from the FDA's level what is really going on out there. I am very concerned that women are dying and these events are not getting reported so that the FDA can actually do their job.

Mr. CUMMINGS. All right. So there have been—and thank you very much. Just a last question. There have been some updates with regard to the warnings, is that right?

Dr. RARICK. Correct.

Mr. CUMMINGS. I think in November 2004, the black box warning was revised and strengthened to add new information on the risk of serious bacterial infections, sepsis, bleeding, and death that may occur following any termination of pregnancy, including Mifeprex. In July 2005, apparently the FDA approved a labeling supplement to again strengthen the black box warning on the product, but noting that atypical presentations of serious infection can occur without fever, bacteria, or significant findings on pelvic exam, etc. Is that accurate?

Dr. RARICK. My review of the label, I believe would agree with that. I have the label here if you want to see the whole label.

Mr. CUMMINGS. No problem. I just wanted to make sure that it is being updated.

Mr. SOUDER. Anything else, Mr. Waxman?

Mr. WAXMAN. This issue of death associated with a drug, when FDA approves drugs, they look at the safety and they look at the efficacy, whether the drug accomplishes what it is intended to accomplish. Aren't there risks associated with a lot of drugs, Dr. Rarick?

Dr. RARICK. Oh, every drug has risks associated with it, yes.

Mr. WAXMAN. Viagra could cause death. Penicillin could cause death. They are on the market. But I assume they are on the market because there is a risk-benefit analysis that even though there may be a rare case of death, it is not so out of control that it diminishes the fact that there is a benefit from those drugs. Is that what we mean by a risk-benefit analysis?

Dr. RARICK. Correct, that you look at those risks, those death reports and rates in contrast to the benefits.

Mr. WAXMAN. There is a question in my mind about deaths or harm associated with a drug as opposed to death or harm caused by the drug. Can you clarify what that means in terms of FDA regulation?

Dr. RARICK. It sounds like a legal term, but I will try. When you think of cause and causation, you think, you know, if I tell my kid, don't touch the hot stove, you are going to get burned, and he touches the hot stove and gets burned, to me, that is cause and effect. When you look at drugs and the risks associated with them, it is very rare that you can actually say X drug causes Y, because, as you know, many, many people take the drugs that don't get that effect. The majority of people who take a particular drug won't have the side effects that are described in the label, but there are going to be side effects in many people, and there, you would call that a side effect that is associated with the use of that product.

Mr. WAXMAN. Well, Mr. Patterson has pointed out, I think appropriately, that he wished his daughter would have known that there was this potential side effect. Now, FDA has issued public health advisories in connection with safety concerns related to Mifepristone in 2004, 2005, and most recently, in March 2006. The FDA has consistently highlighted the fact that the cases of severe infection occurred with regimens of Mifepristone and Misoprostol that were not in approved labeling, although the relationship of the infections to such use remains unknown. What does that mean? Could you tell us more about this, if you know?

Dr. RARICK. That means even though the products are being used outside of their labeled instructions, the FDA wants to make sure that providers and patients are aware that it has been associated with these infections. Whether it would be associated with those infections if it had been used as per label, they are not stating. They are simply saying—they could just say, well, that wasn't used by the label. We don't even need to put it on the label. But instead, they are saying, no, we need to make sure providers and patients are aware that in certain circumstances, we have had these reports. They are not suggesting that it is absolutely that circumstance that caused the increased risk, but they want to make sure that information is available.

Mr. WAXMAN. Well, I thank you for that clarification and I will conclude by saying I just hope the FDA will continue to reevaluate all the evidence, advise people of information that is pertinent, and if they see there is a real threat to this drug, or any other drug, they need to take actions, including taking the drug off the market. But I don't think they ought to act until they look at the science and reach some conclusions on this drug or any other drug.

Thank you, Mr. Chairman.

Mr. SOUDER. Thank you. Rather than ask Dr. Harrison the question again, I think we will insert in the record your earlier response on the causal link, that there were multiple things, including alternatives such as surgical abortions and so on, because you gave a complex answer to that question early on. Did you have anything you want to add?

Dr. HARRISON. No, that is fine.

Mr. SOUDER. Ms. Watson.

Ms. WATSON. I just hope that we can have, Mr. Chairman, a followup hearing as FDA proceeds along its track to assess the risks of this drug, that we will do the oversight that we are responsible for here in Congress, and I would hope that we would base our debate on the results of your studies so that we can come from a scientific base as we discuss this.

So I want to thank the chair for this hearing. I think it has opened up a debate on the efficacy of this drug that has been approved and we need to see what the effects actually are. So thank you so much for the hearing and thanks to the panel.

Mr. SOUDER. Thank you, and I want to thank each of the witnesses and I want to say this directly to Dr. Wood and Dr. Rarick. Whether we agree on the nuances here, or maybe we do long-term or not, that your work long-term, Dr. Wood particularly but also Dr. Rarick, on women's health issues, because certainly it was an area that was underrepresented in the research, and without aggressive advocacy, we wouldn't be where we are on breast cancer, on the whole range of women's health issues. So regardless of where we stand on this issue, I appreciate your lengthy career working with that, Dr. Rarick, as well.

I thank Mr. Patterson for speaking out, Dr. Harrison for giving us that detailed analysis of each of the type of cases and your rigorous analysis of that, and Mr. Snead for bringing the legal aspects in and we will find out, particularly if Danco responds, how to address some of their questions legally on whether they have been following through on the guidelines of FDA.

With that, the subcommittee stands adjourned.

[Whereupon, at 6 p.m., the subcommittee was adjourned.]

[Additional information submitted for the hearing record follows:]

BUC & BEARDSLEY
919 EIGHTEENTH STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20006-5503

WRITER'S TELEPHONE
202-736-3610

TELEPHONE
202-736-3600
FACSIMILE
202-736-3608

October 27, 2006

The Honorable Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy and Human Resources
Committee on Government Reform
House of Representatives
2157 Rayburn House Office Building
Washington, DC 20515-6143

Dear Mr. Chairman:

The enclosed letter from Dr. Richard Hausknecht, Medical Director of our client, Danco Laboratories LLC ("Danco"), responds to the questions in your September 13, 2006 letter to him.

As you will see, in response to certain questions, Dr. Hausknecht has referred you to this cover letter. The reason for his doing so arises from his and Danco's need for confidentiality in certain areas. As you are aware, Danco and everyone associated with the company are faced with the very real threat of violence against them and their workplaces by certain anti-abortion groups and individuals who have publicly threatened Danco and others associated with Mifeprex®. Danco's location, the identity and location of its contract manufacturing facilities, and the identity and locations of other companies and people associated with Danco are subjects of continuing probing by these groups who wish to identify and locate them so they can carry out their threats. To prevent such groups from identifying and locating these individuals and their workplaces, Danco keeps confidential and does not release to the public the names or the locations of those associated with it, nor any information which could lead those bent on violence to the individuals and facilities they have threatened. The Food and Drug Administration also keeps such information confidential, and its doing so has been upheld by the courts. Judicial Watch, Inc. v. FDA, 449 F.3rd 141 (D.C. Cir. 2006). The Court of Appeals has held that information about or leading to the identity and location of Danco and individuals and facilities associated with it could properly be kept confidential as a privacy matter because of the threat of abortion-related violence. The District Court also found that the threat of abortion-related violence was an appropriate basis for refusing to disclose confidential commercial information. 407 F. Supp. 70 (D.D.C. 2005) Danco has therefore instructed Dr. Hausknecht to respectfully decline to answer questions in a manner that would disclose the identity or location or lead to the identity or location of Danco itself and individuals and facilities associated with it.

Danco believes Dr. Hausknecht's responses provide the information necessary to satisfy the public interest in the answers to the questions in your letter, while at the same time honoring the legal and moral obligations of Danco and Dr. Hausknecht to individuals associated with the development, manufacture, and distribution of Mifeprex, who face a threat of physical danger from abortion-related violence.

Your letter also requests copies of Danco's tax returns and information contained in those returns. As a privately held company, Danco has kept such information confidential. Danco therefore respectfully requests that the Subcommittee withdraw its request for this information.

Respectfully submitted,

Nancy L. Buc

Danco Laboratories, LLC P.O. Box 4816, New York, New York 10185

October 26, 2006

The Honorable Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy and Human Resources
Committee on Government Reform
House of Representatives
Congress of the United States
2157 Rayburn House Office Building
Washington, DC 20515-6143

Dear Mr. Chairman:

I am responding to the questions in your September 13, 2006 letter to me.[1] Each response is stated to the best of my knowledge, information, and belief.

The questions are set forth in bold type, my answers in standard type.

1. **What is your title at Danco, and what, specifically, do your responsibilities entail?**

I am a consultant for Danco Laboratories LLC ("Danco") serving as its Medical Director. My responsibilities include management of the Adverse Event Program, pursuant to which I review adverse event information received by Danco, prepare and submit to FDA adverse event reports, as appropriate, and conduct follow up on such reports, as appropriate. I also provide scientific/medical input in reproductive health-related issues, and respond to medical questions from physicians and other healthcare providers.

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[1] The Subcommittee agreed to extend the time for my response to October 27, 2006. Letters dated September 19, 2006 and October 16, 2006 from Buc & Beardsley to Kimberly Craswell, Office Clerk (attached).

2. **Do you currently or did you at any time, either prior to or during your employment with Danco, receive payment of money, favors, travel, accommodations, or any other compensation of any form, for any reason, from Population Council, Planned Parenthood, National Abortion Federation, NARAL, or any other interest group, pharmaceutical company, medical association, or organization other than Danco? If so, which organizations, and why?**

I was employed as the Medical Director of Planned Parenthood New York City from approximately 1996 – 1999. I have received honoraria on two occasions (in 2003 and 2005) from NAF for lectures at its annual national meeting. I received an honorarium for lecturing for Planned Parenthood Connecticut in 2006. I received compensation from The Population Council for participation as an investigator in a clinical trial.

3. **What was the rationale, legal or otherwise, for withdrawing from a Congressional investigative hearing in which your company's product, which is implicated in 8 deaths, 9 life-threatening situations, 232 hospitalizations, 116 transfusion cases, and 88 infections, was a focus? If your lawyers recommend your withdrawal, what was their reasoning?**

Let me first note that to use the word "implicated" in connection with these adverse events states or suggests that Mifeprex® caused such events; there is no scientific basis for such a statement or suggestion.

After initially telling the Subcommittee staff person who contacted me that I would accept the Subcommittee's invitation to testify, I decided upon further reflection not to do so.

4. **Since its inception, Danco has been affiliated with the Population Council, an advocacy group involved in the development of population control technologies throughout the world, particularly in the third world. Please explain in detail Danco's relationship to the Population Council from Danco's inception until now.**

I do not believe that the description of the Population Council in the question provides an accurate or complete picture. As the Population Council's website states, the Council is an international nonprofit organization that conducts biomedical, social science and public health research on a wide range of topics including, among others, reducing neonate and infant mortality, improvement of obstetric care and post-partum care for mothers and newborns, developing strategies to support orphans and other children affected by AIDS, and encouraging abandonment of female genital cutting, as well as examining and improving family planning programs in developing countries.

Danco has a license from the Population Council to market mifepristone in the United States.

5. **It seems Danco was created for the sole purpose of providing chemical abortion to American women by producing Mifeprex. Please name all individuals, corporations, interest groups, government agencies, or other entities which were involved in creating Danco, by providing financial support, consulting, legal services, and any other support.**

Danco was created to bring Mifeprex to the United States, both for medical abortion and to treat other non-pregnancy-related conditions. Also, please see counsel's cover letter.

6. **In addition to chemical abortion being far more dangerous, painful, and inconvenient than surgical abortion in the early weeks of pregnancy, it is our understanding that it is also more expensive.**

I am unaware of any scientific evidence that the medical termination of intrauterine pregnancy ("medical abortion") is any more, let alone far more, dangerous, painful, or inconvenient than surgical abortion.

   a. **What is the standard cost charged by Danco to distributors for one dose of Mifeprex (at both the 200 and 600 mg level), and by physicians to patients?**

   The list price for a pack of 3 - 200 mg Mifeprex tablets is $270. I have no information about physicians' charges to patients.

   b. **What is the cost of a surgical abortion in the case that chemical abortion fails?**

   I have no information about prices charged by providers of surgical abortion.

7. **Often contraceptive suppliers who provide large quantities of product are able to secure reduced rates from distributors in order to increase profits.**

    a. **Is this also the case with chemical abortion? Does Danco supply any providers with Mifeprex at a reduced rate? If so, please list all providers receiving a reduced rate.**

        Danco offers a discount to nonprofit customers and certain high volume customers.

    b. **What benefit does Danco receive in return for the reduced rate?**

        Offering discounts to non-profit organizations and volume discounts is standard in the pharmaceutical industry.

8. **It is our understanding that Danco is incorporated in the Cayman Islands.**

    a. **Is Danco in fact incorporated in the Cayman Islands? If not, where is Danco incorporated?**

        Danco is not incorporated in the Cayman Islands. It is incorporated in the United States.

    b. **Where are Danco's manufacturing facilities?**

        Please see counsel's cover letter.

    c. **Why, if Mifeprex is available only in the United States, would Danco be incorporated in a foreign country?**

        Danco is not incorporated in a foreign country. It is a U.S. corporation.

9. **How many people does Danco employ in the United States? How many people does it employ overall?**

    In the United States and overall, Danco employs six people.

10. **It has been reported that Mifeprex is produced in China at a facility which initially failed FDA inspections several times, leading to significant delays in the availability of Mifeprex chemical abortion in the United States.**

    FDA cannot approve a New Drug Application ("NDA") if "the facilities and controls used for the manufacture, processing and packaging of [such] drug are inadequate to preserve its identity, strength, quality, and purity." 21 U.S.C. § 355 (b)(1)(D). FDA's approval of the Mifeprex NDA means that FDA was satisfied that the statutory standard was met.

a. **Did or does Danco use a Chinese manufacturing facility to produce Mifeprex?**

Please see the cover letter from counsel.

b. **Does Danco monitor the safety of the manufacturing facilities for Mifeprex? If so, how does it go about doing this, and how often does it do this?**

As the sponsor of the NDA for Mifeprex, Danco is responsible for ongoing compliance with FDA's regulations for Good Manufacturing Practices, 21 C.F.R. pts. 210 and 211, which implement provisions of the Food, Drug, and Cosmetic Act directed at drug safety. These "GMP" regulations impose a variety of requirements for manufacturing drugs, including production and process controls, laboratory controls, equipment, and records and reports.

c. **Does the FDA monitor these facilities? If so, how? How often?**

Under the Food, Drug, and Cosmetic Act, FDA has the authority to inspect facilities at which drugs are manufactured. 21 U.S.C. § 374. It has inspected the manufacturing of Mifeprex on several occasions.

11. **Does Danco produce any drugs other than Mifeprex?**

Danco does not market any drugs other than Mifeprex.

a. **Does it have any plans to expand its operations? If so, what are the plans?**

Danco is interested in developing mifepristone for other uses.

12. **Five women who have taken Mifeprex have subsequently died of C. sordellii infection.**

a. **Is Danco aware of any other death from infection by C. sordellii associated with the use of Mifeprex?**

No.

b. **Is Danco aware of any other deaths by infection associated with the use of Mifeprex?**

Danco is aware that a woman died from infection with *Clostridium perfringens* following a medical abortion with Mifeprex. No causal connection between Mifeprex and the death has been established.

c. **What, specifically, has Danco done to investigate the link between Mifeprex and C. sordellii? Other infections?**

Danco has been working with and continues to work with FDA, Centers for Disease Control ("CDC"), healthcare providers, and other medical experts to try and understand the circumstances surrounding these infections that have occurred after childbirth, miscarriage, medical abortion and other ob/gyn-related conditions. Danco obtained and provided FDA with important information about some of the deaths, and continues to respond to questions from FDA.

d. **If there have been any studies or other actions, please name the dates, parameters, and results of such actions.**

On May, 11, 2006, CDC, NIH, and FDA held a public workshop on emerging clostridial diseases, the goal of which was to develop a surveillance and research strategy surrounding *Clostridium difficile* and *Clostridium sordellii.*

13. **If the FDA revoked the approval of Mifeprex for safety concerns related to the 8 deaths, 9 life-threatening situations, 232 hospitalizations, 116 transfusion cases, and 88 infections associated with the use of Mifeprex, would Danco survive as a company? Why or why not?**

If FDA withdrew the approval of Mifeprex, Danco would not be able to market Mifeprex in the U.S. and would not receive revenue from that source. Whether the company would remain viable based on its other drug development programs would remain to be seen.

14. What circumstances, if any, would prompt Danco to refuse to provide Mifeprex to a physician? Has Danco ever cut off sales or refused to provide Mifeprex to a physician?

Mifeprex is not provided to a prescriber unless s/he has signed and submitted an FDA-approved Prescriber's Agreement. As to the second question, prescribers who failed to pay their bills or failed to provide licensing information have had their accounts suspended or terminated.

15. The FDA regulations imposed on the marketing of Mifeprex include the requirement that physicians report all adverse events to Danco.

FDA regulations do not require that physicians report all adverse events to Danco or FDA.

a. What are the details and protocols of your adverse event reporting system?

I review and analyze adverse event information received by Danco from any source including healthcare providers (such as doctors and nurses), patients, physician consultants, manufacturers and marketers of other products, scientific and medical literature, and clinical and non-clinical studies. I evaluate this information to determine what kind of adverse event report, if any, is required to be made to FDA, and fill out FDA's MedWatch Form (FDA Form 3500), if appropriate. A MedWatch Form is submitted to FDA as either a 15-day report or a periodic report, as appropriate. Certain information not reported as a 15-day or a periodic report is included in the annual report to FDA. I also follow up on adverse event information, as appropriate.

b. What would be the usual procedure by which an adverse event would come to your attention?

Danco receives adverse event information via U.S. mail, overnight courier (such as Federal Express), e-mail, fax, or telephone.

c. What proactive measures does Danco take to ensure all adverse events are being reported to the FDA, if any?

Please note that because there is no requirement for physicians or other healthcare providers to report "all adverse events" to Danco or to FDA, the information that Danco receives (see response to question 15a, above) does not necessarily include information about "all adverse events."

Physicians are encouraged to report adverse events to Danco or FDA in several ways:

1. Each shipment of Mifeprex is accompanied by the FDA-approved Prescribing Information, which contains the following:

> Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to:
>
> Medical Director
> Danco Laboratories, LLC
> P.O. Box 4816
> New York, NY 10185
> 1-877-4-Early Option (1-877-432-7596)
>
> For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4-Early Option (1-877-432-7596).

2. The Prescriber's Agreement, which each prescriber must sign and submit before receiving any shipment of Mifeprex, provides Danco's address, 24-hour phone number, and e-mail address and states as follows:

> While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.

3. In Dear Doctor letters to customers (April 19, 2002, November 15, 2004, and July 19, 2005) and to Emergency Room Directors (November 15, 2004 and July 19, 2005). Each of these letters includes a reminder to physicians to report serious adverse events to Danco. One example of the reminder follows:

> We would like to remind you to report any Serious Adverse Events (SAEs) associated with Mifeprex use to the address below. Serious adverse events include death, hospitalization, blood transfusion, and other major events. In the case of on-going pregnancy following treatment with the Mifeprex regimen (approximately 1%), you should also notify us if the patient chooses to proceed with her pregnancy.
>
> Please provide a brief clinical synopsis by writing, calling or emailing:
>
> Medical Director
> Danco Laboratories, LLC
> P.O. Box 4816
> New York, NY 10185
> Medicaldirector@earlyoptionpill.com
> Toll free at 1-877-4 Early Option (1-877-432-7596)

> We may need to contact you to obtain additional information, so please include your contact information. The following information is helpful when you report adverse events: age of patient; gestational age; dosages and means of administration of all medications, including concomitant medications; clinical information on the patient, including relevant past medical history, laboratory results, and health care course; and final outcome of patient.

4. In an "Alert for Healthcare Professionals, Mifepristone (marketed as Mifeprex)" on its website, FDA states "To report any unexpected adverse or serious events associated with the use of [Mifeprex], please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm."

d. Have there been any instances where an adverse event was not reported by Danco to the FDA? What were they?

I believe any adverse event required to be reported has been reported.

16. In an apparent effort to capture reports on the anticipated adverse events that are the result of taking Mifeprex, the FDA's priority approval of Mifeprex included a requirement that prescribing physicians "[m]ust report any hospitalization, transfusion or other serious events to the sponsor or its designate." There is evidence that physicians are not reporting serious events.

The FDA's approval of Mifeprex was not a "priority," "accelerated," or "fast track" approval.

With respect to the statement that there is evidence that "physicians are not reporting serious events," I am not aware of any evidence that physicians are not reporting those serious adverse events of which they become aware.

a. **Planned Parenthood, for example, refers women who receive Mifeprex chemical abortions to a hotline number to call if they experience problems, rather than a number to reach their prescribing physician. That arrangement opens a loophole whereby prescribing physicians many remain unaware of adverse events that take place after they administer the abortion pill, alleviating them of reporting requirements. In light of this, how can Danco assure the public that prescribing physicians are actually reporting all events to Danco?**

Planned Parenthood has in place a separate system for collecting and providing to Danco information from Planned Parenthood clinics about adverse events related to Mifeprex. As a separate matter, neither Danco nor any other pharmaceutical company can ensure that every adverse event is reported to it or FDA, and they are not required to do so.

b. **Danco is required to report all adverse events to the FDA. Is Danco following this requirement? What evidence can Danco provide the Subcommittee which would demonstrate that Danco is reporting all adverse reported to it? This priority approval requirement under Subpart H is meaningless if physicians and emergency rooms are not reporting all adverse events to Danco, as they are required under FDA regulations to do. What does Danco do to ensure that physicians adhere to these reporting requirements? How often are these measures implemented? Please provide any documentation which would provide insight into the nature and frequency of these measures.**

Please see my responses to Question 15 and Question 16 above.

17. **The FDA has acknowledged the deaths of five women by infection associated by the use of Mifeprex, yet the FDA and other claim there has been no causal link established between Mifeprex chemical abortion and C. sordellii infection. If a causal link between the use of Mifeprex and the fatal C. sordellii infection was established, would Danco withdraw Mifeprex from the Market? If not, under what circumstances would Danco withdraw Mifeprex from the market?**

As the question recognizes, FDA and others, including experts from CDC, have stated that no causal link has been established between Mifeprex and *C. sordellii* infection.

The question of the circumstances under which Danco would withdraw Mifeprex from the market is too hypothetical to be answered.

18. The consensus among scientists who presented at the May 11, 2006 CDC conference was that mifepristone compromises the immune response, which would explain the 5 reported deaths by C. sordellii infection, 88 other reported infections, and several of the other nine life-threatening events.

I respectfully disagree that the consensus was as stated in the question. To the contrary, the consensus at the conference was that there is a lack of data about the cause, risk factors, or mechanism of action of *C. sordellii.*

a. What is Danco's opinion on the work of physicians like Dr. James McGregor, Dr. Esther Sternberg, and Dr. Ralph Miech, which identify a mechanism by which Mifeprex inhibits the immune system?

There are no scientific data identifying such a mechanism of action.

b. In what ways, specifically, might this research be refuted? Are there any methodological flaws, or flaws in the analysis of the data? If not, doesn't this work have serious implications for our understanding of Mifeprex's safety?

There are no scientific data supporting the hypothesis to evaluate or refute.

19. Despite the multitude of known adverse events associated with Mifeprex chemical abortions and acknowledged by the FDA, including 8 deaths, 9 life-threatening situations, 232 hospitalizations, 116 transfusion cases, 88 infections, and the fact that it is at least ten times more fatal than early surgical abortion,[2] it is still available on the market. Furthermore, the FDA's Medical Review, finalized on November, 1999 stated,

> **"[t]his method of pregnancy termination is of limited value because of the relatively short window of opportunity, [sic] in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the**

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[2] **[The following footnote is from the question in Chairman Souder's letter.] The mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available to women. Dr. Michael Green, based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. *See*, Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318. Current numbers suggest, however, eight deaths in the United States, while, according to the manufacturer, 575,000 women have used the drug. This works out to 1 in about 71,875, or 1.39 for every 100,000, suggesting a Mifeprex fatality rate that is fourteen times greater than that with surgical abortion during the eight weeks of pregnancy.**

last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This then, leaves only a three week period for the women to secure this method of abortion.

"Another disadvantage of this method ...is the need for at least three visits to the medical facility [sic] including at least a four hours [sic] stay after the administration of the misoprostol.

"In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans ...

"[In a study comparing medical and surgical abortion,] [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion ...Specific symptoms and adverse events, include cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients ...Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients.

"[In another study of 377 patients comparing mifepristone to surgical abortion} [f]our mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine mifepristone patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding...Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients...Mifepristone patients reported significantly longer bleeding in all three gestational age groups. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients...Mifepristone patients were routinely offered oral narcotics for expulsion-related pain, and 78.5% used them. Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of

> **mifepristone patients compared with only 10.5% of surgical patients. Nausea or vomiting in the follow-up interval was common in the mifepristone group, but rare among surgical patients."**

To an outside observer, it seems the only benefit of choosing Mifeprex is the opportunity to avoid a surgical procedure that is less painful, more convenient, quicker, and exponentially safer than its chemical alternative. Please explain Danco's perspective about what benefits a women might gain from choosing a Mifeprex chemical abortion and explain how these benefits outweigh the increased inconvenience, the increased discomfort, and the increased danger of deadly infection, massive hemorrhage, and death associated with Mifeprex.

The question includes a multitude of assumptions and implicit and explicit assertions which are incorrect. Without attempting to parse each and every one, I note several as follows. No causal connection has been found between Mifeprex and any death. The numbers cited regarding various adverse events reflect reports made to FDA, none of which is a determination of a causal connection. Also, there is no requirement of a 4-hour stay after the administration of misoprostol in the FDA-approved regimen.

To answer the question as to why women choose Mifeprex, a number of studies document that many women offered a choice of a medical or surgical abortion choose medical abortion. For example, in a review of 12 published studies on patient attitudes toward medical abortion, the author concluded that, in most trials that offered a choice between surgical abortion and medical abortion, 60-70% chose medical abortion (Winikoff, B. et al., Acceptability and Feasibility of Early Pregnancy Termination by Mifepristone-Misoprostol: Results of a Large Multicenter Trial in the United States, *Arch Fam Med* 360, July/Aug 1998). Those studies did not collect data on the reason for each woman's choice, but there are several studies that have investigated the reasons many women choose medical abortion over surgical abortion. Some of those reasons are personal control, avoidance of surgery, privacy, and naturalness (e.g., Fielding et al., Having an Abortion Using

Mifepristone and Home Misoprostol: A Qualitative Analysis of Women's Experiences, *Perspectives on Sexual and Reproductive Health* 34(1): 34 – 40, 2002).

20. Please provide detailed summaries of all postmarket studies which Danco has conducted on Mifeprex, for any reason, the purpose of each study, and the results, specially noting for the Subcommittee which of these studies were required by the FDA.

FDA's approval of Mifeprex included a requirement that Danco conduct two post marketing studies. The first is a pregnancy outcome follow-up study of women who continued to be pregnant for at least one month after any Mifeprex exposure. The second is a prescriber monitoring study that was designed primarily to assess the relationship between patient outcome and whether the prescriber (a) provided surgical intervention if the medical abortion was not successful, or (b) referred patients to another healthcare provider for surgical abortion if the medical abortion was not successful.

Danco designed and implemented a protocol and is currently conducting the pregnancy follow-up study. Danco has determined that as of this time, very few pregnancies were continued for at least one month. The company has also designed and implemented a protocol for the prescriber monitoring study. Thus far, few Mifeprex prescribers have expressed an interest in participating in the study.

Danco provides updates to FDA on these two studies, including in Annual Reports.

21. Please explain in detail Danco's risk management plan for Mifeprex, FDA's efforts to ensure its implementation, and Danco's compliance with the risk management plan. Please provide any relevant documentation.

In addition to risk management practices required of all sponsors of new drugs under FDA's regulations (21 C.F.R. § 314.80), FDA's letter approving Mifeprex restricted distribution in a number of respects that are components of Danco's risk management plan.

Copies of the approval letter and other documents on this issue (e.g., Prescriber Agreement, Patient Agreement, and Medication Guide) are attached.

a. How often does FDA conduct investigations into Danco's compliance with the restrictions and regulations imposed with the approval of Mifeprex?

I am aware of five such FDA audits. I do not know if FDA has performed other investigations of Danco's compliance that do not involve such audits.

b. Which restrictions and regulations do these investigations cover?

I do not know what the audit teams' charters have been, but when auditing Danco, FDA has generally reviewed adverse event reporting records. FDA has also reviewed shipping and storage records, and Prescriber Agreement records.

c. Do they investigate compliance with all regulations during every investigation, or only some?

With respect to Danco, and as far as I know, other drug companies, only some.

d. If only some, which restrictions or regulations, and how often?

See b above.

e. Who conducts the investigations, and how are they conducted?

FDA personnel perform the audits under FDA's procedures for performing audits.

f. What are the specific dates and parameters of each investigation the FDA has conducted?

FDA audited Danco March 6-13, 2006, September 20-28, 2004, and in June 2002. FDA audited Danco's logistics partner in 2002 and the authorized distributor in 2002.

g. **What were the results for each investigation? Did the FDA notify Danco that it was in full compliance with all restrictions and regulations? If not, of which restrictions or regulations was Danco considered noncompliant?**

No warning letters have been issued or enforcement action taken in connection with these audits. It is not FDA's practice to notify companies that they "are in full compliance with all restrictions and regulations." No questions were raised by FDA about compliance with restrictions on distribution. Certain questions were raised about 21 C.F.R. § 314.80. FDA provided Danco with a copy of its inspectional observations from each audit of Danco on an FDA Form 483. Danco believes that most of these inspectional observations were inappropriate. FDA had no inspectional observations and no Form 483 was issued by FDA after the inspection of the logistics partner.

22. **Is Danco notified in advance each time FDA investigates Danco's compliance, or has Danco been subject to unannounced compliance checks for any restriction/ regulation imposed with the Mifeprex approval?**

Certain audits have been announced in advance.

a. **If such unannounced compliance checks/ investigations have occurred, please provide dates and the subject or regulation/ restriction(s) investigated.**

An unannounced FDA audit of Danco occurred in September 2004. FDA reviewed adverse event reporting records.

23. **Has Danco or the Population Council been subject to any lawsuits related to Mifeprex? If so, when, and on what grounds?**

Danco and Population Council have been named in three cases. One was filed in September 2004, one in December 2004, and one in September 2005. All allege personal injury. Danco and the Council have denied the allegations. It is possible that Population Council has been named in other lawsuits of which I am unaware.

24. The September 28, 2000 memo accompanying the Subpart H approval of Mifeprex says, "The signed [patient] agreement form will be given to the patient for her reference and another kept in the medical record. The Population Council has committed to auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms."

The language about auditing prescribers pertains to one of the Phase IV ongoing study commitments. In that prescriber monitoring study (which is described in my response to Question 20) one of the secondary objectives was to assess the frequency at which patients and providers sign a Patient Agreement form.

a. Has Danco Laboratories performed any of the aforementioned audits? How often? When?

No, because the study has not been enrolled.

b. Has Danco shared the results of these audits with the FDA?

Not applicable.

c. Please provide a summary of all findings.

Not applicable.

25. The approval of Mifeprex included a requirement that Danco have the ability to track Mifeprex usage "to the patient level."

a. Does such a tracking system exist?

Yes.

b. **If so, what are the exact numbers of unique patients who have taken the drug, and individual doses dispensed to patients? Please break the numbers down by year.**

The tracking system is not designed to and does not yield this information. Danco estimates that approximately 650,000 women have used Mifeprex in the United States since approval in 2000.

c. **If Danco does not have exact numbers as required in the approval for Mifeprex, please explain in detail why not.**

The approval does not require that Danco have exact numbers.

26. If there is a reliable tracking system in place, why does Danco estimate usage of its product? Why doesn't Danco use the requirement to track its product to the patient level to calculate precise usage numbers? Couldn't estimated usage numbers result in potential chemical abortion patients perceiving a lower risk associated with the use of Mifeprex? Shouldn't Danco take appropriate steps to ensure patients are giving fully-informed consent?

As to the first two questions, please see the answers to Question 25 above. Danco believes patients are given accurate risk information.

The concept of "fully-informed consent" applies to subjects in a clinical trial, not to patients to whom an approved drug is prescribed by their physician. Patients receive an FDA-approved Medication Guide and Patient Agreement before deciding whether to take Mifeprex. If a patient decides to use Mifeprex for a medical abortion, she reads and signs an FDA-approved Patient Agreement, acknowledging among other things, that she has read the Medication Guide and discussed the risks and benefits with her provider.

27. The Mifeprex label suggests that infections and hemorrhage are expected complications of chemical, surgical, and spontaneous abortion alike. Data shows, however, that chemical abortion is associated with a much higher risk of infection, hemorrhage, and death than its counterparts at the early stages of pregnancy. Isn't this label, then, misleading? Shouldn't Mifeprex labeling reflect the fact that chemical abortion is far more dangerous than surgical or spontaneous abortion? If not, why not?

The label is not misleading. There is no need or requirement to provide comparison to alternative treatments. There is no evidence that medical abortion is associated with a higher, much less "much higher," risk of infection, hemorrhage, and death than surgical abortion. The FDA-approved Mifeprex Prescribing Information provides extensive information about the drug, including safety and efficacy data, and the FDA-approved Medication Guide describes the possible risks and side effects in lay terms for patients.

28. What were Danco's profits for each of the past six years since its inception? Please provide to the Subcommittee copies of all annual company reports and/or all I.R.S. tax fillings by Danco for the past six years.

Please see counsel's cover letter.

Respectfully submitted,

Richard U. Hausknecht, M.D.

SEP 28 2000

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

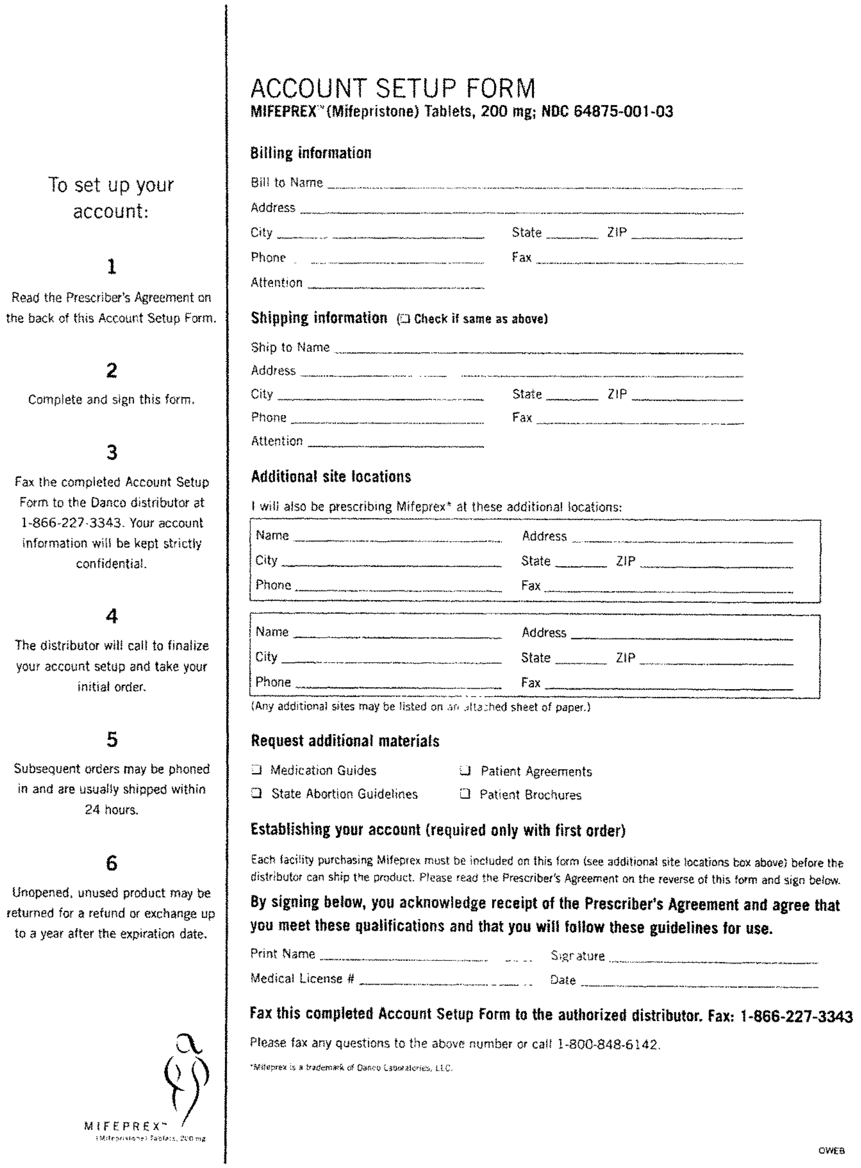
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call [redacted]

Sincerely,

/S/
[redacted]
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL



To set up your account:

1

Read the Prescriber's Agreement on the back of this Account Setup Form.

2

Complete and sign this form.

3

Fax the completed Account Setup Form to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.

4

The distributor will call to finalize your account setup and take your initial order.

5

Subsequent orders may be phoned in and are usually shipped within 24 hours.

6

Unopened, unused product may be returned for a refund or exchange up to a year after the expiration date.

MIFEPREX™
(Mifepristone) Tablets, 200 mg

ACCOUNT SETUP FORM

MIFEPREX™ (Mifepristone) Tablets, 200 mg; NDC 64875-001-03

Billing information

Bill to Name ____________________
Address ____________________
City ____________ State ______ ZIP ________
Phone ____________ Fax ____________
Attention ____________

Shipping information (☐ Check if same as above)

Ship to Name ____________________
Address ____________________
City ____________ State ______ ZIP ________
Phone ____________ Fax ____________
Attention ____________

Additional site locations

I will also be prescribing Mifeprex* at these additional locations:

Name ____________ Address ____________
City ____________ State ______ ZIP ________
Phone ____________ Fax ____________

Name ____________ Address ____________
City ____________ State ______ ZIP ________
Phone ____________ Fax ____________

(Any additional sites may be listed on an attached sheet of paper.)

Request additional materials

☐ Medication Guides
☐ State Abortion Guidelines
☐ Patient Agreements
☐ Patient Brochures

Establishing your account (required only with first order)

Each facility purchasing Mifeprex must be included on this form (see additional site locations box above) before the distributor can ship the product. Please read the Prescriber's Agreement on the reverse of this form and sign below.

By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name ____________ Signature ____________
Medical License # ____________ Date ____________

Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*Mifeprex is a trademark of Danco Laboratories, LLC.

OWEB

MIFEPREX™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.
- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

*MIFEPREX is a trademark of Danco Laboratories, LLC.

PATIENT AGREEMENT
Mifeprex® (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex* and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
    - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
    - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
    - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
    - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
    - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
    - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: ______________________________

Patient Name (print): ______________________________

Date: ______________________________

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: ______________________________

Name of Provider (print): ______________________________

Date: ______________________________

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05
* Mifeprex is a registered trademark of Danco Laboratories, LLC.

MEDICATION GUIDE

Mifeprex® (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases in which misoprostol was used in the vagina. There is no information that vaginal use of misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is

____________________________.

Be sure to contact your provider promptly if you have any of the following:

> **Heavy Bleeding.** Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.
>
> **Abdominal Pain or "Feeling Sick".** If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
>
> **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that they understand that you are having a medical abortion with Mifeprex.

---

* Mifeprex is a registered trademark of Danco Laboratories, LLC.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this MEDICATION GUIDE.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

* * *

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 2: 7/19/05

Danco Laboratories, LLC

P.O. Box 4816
New York, NY 10185

1.877.4 EARLY OPTION
(1.877.432.7596)

www.earlyoptionpill.com

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BERNARD SANDERS, VERMONT,
INDEPENDENT

September 6, 2006

O. Carter Snead
Associate Professor of Law
University of Notre Dame
311 Law School
P.O. Box 780
Notre Dame, IN 46556

Re: Subcommittee Hearing, "RU-486: Demonstrating a Low Standard for Women's Health?"

Dear Mr. Snead:

Thank you very much for your testimony on May 17, 2006, before the Subcommittee on Criminal Justice, Drug Policy and Human Resources. Due to the limited amount of time available for the hearing, we were unable to address all of the issues involved. To better help the Subcommittee understand these significant issues, we are submitting to you the attached list of questions for the record.

In order to help the Subcommittee move forward with its work on this subject, we request that you respond to these questions in writing no later than the close of business on Friday, September 22, 2006. Your answers will be included in the written record.

Thank you very much for your time and assistance. If you have any questions, you may have a member of your staff contact Kimberly Craswell at 202-225-2577.

Sincerely,

Mark Souder

Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy and Human Resources

Enclosure

1. If the FDA was to pull RU-486 from the market, it is likely the issue will be litigated. What are some of the potential legal theories which might be the subject of future lawsuits, and do these legal theories have merit?

2. How is a drug withdrawn using an "imminent hazard" test, and how broadly has "imminent hazard" been interpreted by the courts? It appears to be quite rare that a drug is withdrawn from the market without the voluntary cooperation of the manufacturer. Why might this be the case? Are you familiar with any situation where a drug was forcibly withdrawn by the FDA? If so, what was the outcome?

3. What kind of deference is accorded to the Secretary of HHS when courts review his or her finding of "imminent hazard"?

4. What if there is a division of respectable medical authority on the presence or absence of an imminent hazard?

To: Chairman Mark E. Souder
From: Professor O. Carter Snead
Re: Subcommittee Hearing, "RU-486: Demonstrating a Low Standard for Women's Health?" [Responses to Written Questions]
Date: September 22, 2006

Question 1: FDA's authority to withdraw RU-486 and potential challenges

If the FDA were to remove RU-486 from the market, the legal issues that would arise depend entirely on the mechanism used by FDA to achieve this result. It is thus difficult to answer this question in the abstract. Put most generally, the questions presented would relate to whether or not the FDA possesses the statutory authority to take such action. If such authority were found, litigants would perhaps challenge the nature and scope of the FDA's action pursuant to such authority. As I mentioned in my testimony, FDA has numerous sources of authority to withdraw products from the market. It could invoke the traditional withdrawal provisions authorized by Section 505 of the Food, Drug and Cosmetic Act (along with the relevant implementing regulations). Because RU-486 was approved under Subpart H, FDA has additional authority at its disposal to withdraw this product, provided that the regulatory criteria are satisfied.

As I mentioned in my testimony, grounds for withdrawal under the traditional approach include a finding (following notice and an opportunity for a hearing) that: (i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or (ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or (iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in § 314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or (iv) That the application or abbreviated application contains any untrue statement of a material fact; or (v) That the patent information prescribed by section 505(c) of the act was not submitted within 30 days after the receipt of written notice from FDA specifying the failure to submit such information.

Under the relevant withdrawal provisions of Subpart H, the FDA can (following notice and an opportunity for a hearing) withdraw approval for any of the following reasons: (1) A postmarketing clinical study fails to verify clinical benefit; (2) The applicant fails to perform the required postmarketing study with due diligence; (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) The applicant fails to adhere to the postmarketing restrictions agreed upon; (5) The promotional materials are false or misleading; or (6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.[1]

If FDA were to invoke the above provisions to remove RU-486 from the market, adverse litigants would likely challenge the application of the relevant criteria to the factual circumstances presented. It would be impossible to judge the merits of such challenges without a concrete set of facts.

Question 2,3 and 4: Imminent Hazard Authority

As I mentioned in my testimony, the "imminent hazard" authority authorizes Secretary of Health and Human Services to suspend approval of an application and then afford the applicant an opportunity for an expedited hearing."[2] This authority, vested solely in the Secretary of HHS (i.e., it is nondelegable), is perhaps the most dramatic mechanism that could potentially be wielded against mifepristone.

Given its sweep and force, it is a little surprising that "imminence" is not defined narrowly. The seminal case in this domain held that "imminence" is "not to be restricted to a concept of crisis."[3] The term is defined and the criteria to be considered are set forth in 21 CFR 2.5:

> (a) Within the meaning of the Federal Food, Drug, and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists.
>
> (b) In exercising his judgment on whether an imminent hazard exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.

As with all of the aforementioned mechanisms for withdrawal, the Secretary's "imminent hazard" authority is ultimately subject to judicial review. But, as with the aforementioned means of withdrawal discussed above, courts are enormously deferential to the Secretary's conclusions in this context. As the court in *Forsham* made clear, to reverse the Secretary's decision, the challenging party must demonstrate "a substantial likelihood that the decision was a clear error of judgment and that [the Secretary] failed to articulate any rational connection between the facts submitted to him and the choice he made."[4] The District Court will only reverse the decision if it finds that the decision in question was "arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with the law."[5] This is an enormously high burden for the challenging party to sustain. It is made more difficult by the court's further holding that the challenging party will not prevail merely by demonstrating that there is a difference of opinion among "respectable scientific authority" on the question of whether the hazard can be properly characterized as "imminent." [6] Nor can the challenging party prevail by noting that the evidence relied upon by the Secretary "had [previously] been available for some length of time."[7]

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[1] *Id.*
[2] *Id.*
[3] *Forsham v. Califano*, 442 F. Supp. 203 (D. D.C. 1977)(this case appears to be the only instance in which the "imminent hazard" authority of the HHS Secretary has invoked).
[4] *Id.*

Turning to the present case, if the Secretary of Health and Human Services were convinced that mifepristone presented a serious risk to public health, he or she could invoke this rarely used provision to immediately suspend its approval. If *Forsham* is a reliable guide, it is likely that such a decision would receive maximal deference from the courts (provided the decision was rooted in persuasive evidentiary support).

Final Thoughts:

The most pressing question, in my view, raised by the hearing is whether and to what extent Danco Laboratories has complied with the conditions of approval imposed by Subpart H. The regulations prescribed by Subpart H were devised to expedite the approval of drugs intended to treat "serious or life-threatening illnesses," where such drugs imposed a greater than normal acceptable risk to the patient. That is, Subpart H was designed in part as an alternative means of approval for useful drugs that would otherwise fail the traditional risk/benefit calculus required for FDA approval. Subpart H facilitated approval of such risky (but apparently useful) drugs by imposing additional postmarketing restrictions above and beyond what was required through the normal mechanisms of approval.[8] In this way, the FDA was able to add another factor in favor of approval to the risk/benefit calculus. As the FDA explained in its Final Rule adopting Subpart H: "For drugs approved under the accelerated procedure regulations, the risk/benefit assessment is dependent upon the likelihood that . . . postmarketing restrictions will enable safe use."[9] In other words, the postmarketing restrictions "aim to enhance the safety of a drug whose risks would outweigh its benefits in the absence of restriction."[10]

Given the central importance of the postmarketing restrictions possible under Subpart H, it is not surprising that the failure to comply with such restrictions, or a showing that such restrictions are inadequate to assure safe use of the drug, result in an expedited withdrawal of the drug's original approval. As the FDA noted in its Final Rule, "If . . . restrictions do not lead to safe use, the risk/benefit assessment for these drugs changes significantly. FDA believes that if that occurs, rapid withdrawal of approval as set forth in this rule is important to the public health."

In short, the FDA offered Danco an option for accelerated approval of RU-486 the cost of which was submission to additional restrictions. **FDA has an obligation to vigorously investigate**

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[5] *Id.*

[6] *Id.*

[7] *Id.*

[8] *See* 21 CFR 314.520. *See also*, 57 FR 58942 (explaining that Subpart H applied to those circumstances where "FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted.").

[9] 57 FR 58942, 58955.

[10] *Id.* at 58952.

whether Danco is in compliance with the relevant postmarketing restrictions, or in the alternative, whether such restrictions are inadequate to guarantee the safety and efficacy of RU-486. FDA would be justified in withdrawing approval if any of the following reasons obtain: (1) A postmarketing clinical study fails to verify clinical benefit; (2) The applicant fails to perform the required postmarketing study with due diligence; (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) The applicant fails to adhere to the postmarketing restrictions agreed upon; (5) The promotional materials are false or misleading; or (6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.[11]

In my opinion, the Subcommittee should pursue answers to these questions as a first priority in undertaking their oversight responsibilities.

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[11] *Id.*

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September 13, 2006

Lisa D. Rarick, M.D.
RAR Consulting, LLC
215 Midsummer Circle
Gaithersburg, MD 20878

Re: Subcommittee Hearing, "RU-486: Demonstrating a Low Standard for Women's Health?"

Dear Dr. Rarick:

Thank you very much for your testimony on May 17, 2006, before the Subcommittee on Criminal Justice, Drug Policy and Human Resources. Due to the limited amount of time available for the hearing, we were unable to address all of the issues involved. To better help the Subcommittee understand these significant issues, we are submitting to you the attached list of questions for the record.

In order to help the Subcommittee move forward with its work on this subject, we request that you respond to these questions in writing no later than the close of business on Friday, September 22, 2006. Your answers will be included in the written record.

Thank you very much for your time and assistance. If you have any questions, you may have a member of your staff contact Kimberly Craswell at (202)-225-2577.

Sincerely,

Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy and Human Resources

Enclosure

1. The FDA has acknowledged the deaths of eight women, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection associated with mifepristone (marketed in the U.S. as Mifeprex, also known as RU-486). Is it reasonable to be concerned about the apparent danger this drug poses to women? Why or why not? If so, how should this concern manifest itself? When, and under what circumstances, should it manifest itself in the removal of mifepristone from the market?

2. The consensus among the scientists who presented at the May 11, 2006 CDC conference was that mifepristone compromises the immune response, which would help to explain the five deaths by C. Sordellii infection, 88 other infections, and several of the other nine life-threatening events. Your own testimony, as the Democrats' witness, is in conflict with that consensus.

    a. What is your opinion on the work of physicians like Dr. James McGregor, Dr. Esther Sternberg, and Dr. Ralph Miech, which identifies a mechanism by which mifepristone inhibits the immune system?
    b. In what ways, specifically, might this research be refuted? Are there any methodological flaws, or flaws in the analysis of the data? If not, doesn't this work have serious implications for our understanding of mifepristone's safety?

3. FDA has acknowledged 116 blood transfusions in association with the mifepristone drug regimen. In the U.S. trial alone there was one case of bleeding for 69 days, and another case of a woman bleeding for 45 days. Studies have shown there is a significantly lower risk of hemorrhage resulting from surgical abortion than there is for chemical abortion. Are you aware of another drug or drug regimen which causes a similar amount of bleeding for similar amounts of time? In your opinion, how many transfusion cases would there have to be to demonstrate that the cost associated with this drug outweighs the benefit and to withdraw it?

4. A memo, concerning the mifeprex approval application, dated May 7, 1996 from the FDA Center for Drug Evaluation and Research to the Population Council states the following:

    > "We...refer to our acknowledgement letter dated March 20, 1996, which stated that the review priority standard for this application would be Standard (S)...Upon further consideration of your application, we have concluded that it should receive a Priority (P) review."

Furthermore, your own approvable letter of September 17, 1996, stated "[t]he review team has worked hard on this *priority* application." (emphasis added).

a. The decision to assign priority review status to a drug is based on whether "The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease."[1] Please explain the FDA's treatment of pregnancy as a disease in this instance. Please also name other drugs that have been assigned Priority review status for other conditions that are clearly not diseases.
b. As the Democrats' witness, significant parts of your oral testimony were devoted assuring the Subcommittee that Subpart H was not imposed to prioritize the approval process. It turns out, however, that mifepristone did receive a priority review, if not through Subpart H. Why weren't you forthcoming about FDA's granting of this special status to mifepristone?
c. FDA documents show that medicines selected for priority review have a goal of a six month review period. The Division of Reproductive and Urologic Drug Products met that goal by issuing an approvable letter September 17, 1996. What happened after this approvable letter? Why wasn't the drug made available in 1996?
d. What is the nature of the drugs reviewed at the same time as mifepristone which did *not* receive priority review status? Weren't there other drugs more deserving of Priority attention from the FDA than mifepristone, for which a safer alternative is already available?
e. It is my understanding that the fee charged to a drug company for the review of a drug is contingent upon the review status it receives, and that "the review priority classification assigned at the time of filing will not change during the first review cycle and the user fee time frame of the original review cycle will be that based on the original priority." Was the Population Council's review fee less for the Priority review of mifepristone than if the Priority standard had been assigned at the beginning of the drug's review?
f. By what process was the review standard changed from Standard to Priority? Was this change initiated by the FDA or by the Population Council? Please explain in detail how

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[1] Center for Drug Evaluation and Research, Manual of Policies and Procedures § 6020.3 (1996).

this change came about. Please also provide all documentation related in any way to the original decision to assign Standard review status to mifepristone and the later change in its status to Priority review.

5. The Division of Reproductive and Urologic Drug Products (the Division), which reviewed the mifepristone application, was created in 1996, the same year that the Population Council submitted its New Drug Application for mifepristone.

    a. How many people worked under you in the Division?
    b. How many people work in other Divisions in the Center for Drug Evaluation and Research?
    c. Did the creation of the Division reduce the amount of time that otherwise would have been spent on processing the mifepristone NDA, had the Division not been created?
    d. Please list all other drugs that the Division reviewed during the time period from the submission of the mifepristone NDA, March 16, 1996, to your first approvable letter, dated September 17, 1996.
    e. What other approvable letters did your division issue during that same time period?
    f. What other products was your division responsible for reviewing in the time period after the first mifepristone approvable letter until your departure from the Division in December of 1999? What was the outcome of each NDA?

6. In the Clinical Postmarketing Safety Review for mifepristone, dated November 15, 2004, Section 5.3.2 Review of Medical Literature for Safety of Alternative Mifepristone and Misoprostol Dosing Regimens, the FDA stated:

    > "The DRUDP [Division of Reproductive and Urologic Drug Products] conducted a MEDLINE search to evaluate the relative safety of the alternative dosing regimens of mifepristone and misoprostol, focusing on the commonly used 'off-label' regimen of mifepristone 200mg with 800µg intravaginal misoprostol. *Of particular interest were randomized, controlled trials.*" (Emphasis added.)

    In your oral testimony as the Democrats' witness, you indicated that randomized trials were unwise. If it is unwise or unnecessary, why would the FDA be interested in seeing studies that subjected women to unnecessary inconvenience? Why if randomized studies are desirable, were they not required in the case of mifepristone, especially since the health of women was at stake?

7. The FDA has acknowledged the deaths of eight women, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection associated with mifepristone.

    a. Please identify the negative consequences, if any, to women if mifepristone was withdrawn from the market pending an investigation into its link to C. Sordellii. Would you oppose this action? Why or why not?
    b. If a causal link between the use of mifepristone and the fatal C. Sordellii infection was established, would you support the withdrawal of this drug?

8. Despite the multitude of known adverse events associated with mifepristone chemical abortions and acknowledged by the FDA, including 8 deaths, 9 life-threatening situations, 232 hospitalizations, 116 transfusion cases, 88 infections, and the fact that it is at least ten times more fatal than early surgical abortion,[2] it is still available on the market. The FDA justifies the continued availability of mifepristone by referring to a risk / benefit analysis.

    a. The fatality rate for mifepristone is far greater than a surgical abortion in the first eight weeks of pregnancy. Furthermore, the FDA's Medical Review, finalized on November 22, 1999 stated,

        > "[t]his method of pregnancy termination is of limited value because of the relatively short window of opportunity, [sic] in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.
        >
        > "Another disadvantage of this method…is the need for at least three visits to the medical facility [sic] including at least a four hours [sic] stay after the administration of the misoprostol.

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[2] The mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available for women. Dr. Michael Green, based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. *See,* Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318. Current numbers suggest, however, eight deaths in the United States, while, according to the manufacturer, 575,000 women have used the drug. This works out to 1 in about 71,875, or 1.39 for every 100,000, suggesting a Mifeprex fatality rate that is fourteen times greater than that with surgical abortion during the eight weeks of pregnancy.

> "In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans...
>
> "[In a study comparing medical and surgical abortion,] [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion...Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients...Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients.
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> "[In another study of 377 patients comparing mifepristone to surgical abortion] [f]our mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine mifepristone patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding...Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients...Mifepristone patients reported significantly longer bleeding in all three gestational age groups. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients...Mifepristone patients were routinely offered oral narcotics for expulsion-related pain, and 78.5% used them. Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients. Nausea or vomiting in the follow-up interval was common in the mifepristone group, but rare among surgical patients."

To an outside observer, it seems the only benefit of choosing mifepristone is the opportunity to avoid a surgical procedure that is less painful, more convenient, quicker, and exponentially safer than its chemical alternative. As the Democrats' witness, explain what benefits a woman might gain from choosing a mifepristone chemical abortion, and explain how these benefits outweigh the increased inconvenience, the increased discomfort, and the increased danger of infection, hemorrhage and death associated with mifepristone.

b. Based on your knowledge and experience, is it uncommon for drugs to be withdrawn from the market while manufacturers investigate severe adverse reactions? Please provide some examples.
c. Based on your knowledge and experience, is it uncommon for drugs to be withdrawn from the market when an association, rather than a causal relationship, with adverse events is identified? Please provide some examples.

9. In your testimony as the Democrats' witness you state that "the public can only have confidence in the FDA's conclusion if it knows that it is impervious to political pressure." The FDA functions as a reactive, not a proactive agency. It does not develop drugs itself, but rather investigates the safety and efficacy of drugs once a pharmaceutical industry files for approval of a drug. In the case of RU-486, however, President Clinton, HHS, the FDA, and the Department of State were involved in negotiations to bring the drug to the United States before any NDA was even filed. Furthermore, memos suggest that many of the scientific decisions about this drug were made before any New Drug Application was filed.

    a. By your own logic, then, isn't it reasonable for the public *not* to have confidence in the approval of RU-486, given that the approval process began only after political pressure was brought to bear by the Clinton Administration?
    b. Were you aware of the President or the Administration's involvement in bringing RU-486 to the U.S. when you were involved in the drug's approval?
    c. Are you aware of anyone from the Clinton Administration outside of the FDA communicating with the FDA at any level regarding the mifepristone approval at *any* time before or during the approval of the drug? If so, please characterize the nature of each communication?

10. A memo of reprimand with a handwritten date of January 22, 1997 from the Clinical Investigations Branch Division of Scientific Investigations, Office of Compliance from the Center for Drug Evaluation and Research, stated in reference to two French trials for mifepristone:

> "From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you did not adhere to all good clinical investigational practices governing your conduct of the clinical investigations and the protection of human subjects. At the

> close of the inspection, the FDA auditors presented you with a form FDA 483 which listed their observations. These included failure to follow the protocol in that subjects who smoked, were over 35 years of age, and exhibited lengths of amenorrhea greater than that allowed by the protocols were entered into the study. In addition, some laboratory and ultrasound reports could not be located in both studies."

a. Please explain what an FDA 483 form is, and what implications it might have for a drug trial.
b. Were the studies mentioned in this memo the French trials upon which the approval of mifepristone was based?
c. What were the details of all of the violations which the Clinical Investigations branch noted in their investigation? Please provide all relevant documentation.
d. This reprimand was not mentioned in the Advisory Committee hearing or any other FDA documents, although the inspection was carried out beforehand. Has the FDA made any public statements about this reprimand? If not, why, considering that this study was so critical to the approval of mifepristone, and this is such a critical women's health issue?
e. Has the FDA looked into whether the documents lost were of women who experienced adverse events?
f. In both French trials, participants were excluded because "neither an ultrasound nor a beta subunit HGC pregnancy test was performed to confirm pregnancy." The FDA reprimanded the researchers for losing ultrasound and lab reports. Is it possible that these women were excluded because these records were lost, rather than the reason given—that a pregnancy test was never performed? It seems rather unlikely clinicians would fail to test women to see if they were pregnant. Do the numbers of those excluded correspond to the numbers of records lost?
g. Does FDA often approve drugs on the basis of trials which do not adhere to good clinical investigational practices? Does it ever? If so, please provide examples.

11. On September 17, 1996, you issued a memorandum as Division Director that the priority application for mifeprex is approvable. On September 18, 1996, the Center for Drug Evaluation and Research, after reviewing the Mifepristone application, issued an approvable letter. The determination was made in spite of the fact that the application relied on two French trials which the FDA had reprimanded and a U.S. trial that had not been completed. The FDA Medical Officer's Review of U.S. Safety Data dated July 14, 1996, noted

"It is not possible to make a complete comparison of the serious adverse events reported in the United States trial and the pivotal French studies in the NDA, due to *different definitions of SAEs and different adverse event reporting requirements in the two countries.*" (emphasis added).

a. Why, if France has different adverse event reporting requirements, is their data on adverse events acceptable as the sole basis for an approvable letter from the Division?
b. Why, since the French trials had been compromised, wasn't another U.S. trial recommended?
c. Why, if the French trials were adequate to recommend its use among the American population, as the Division's approval of the mifepristone application before the completion of the U.S. trials suggests, was a trial even conducted in the United States?
d. Why didn't the FDA wait until the completion of the U.S. trial to hold the Advisory Committee hearings?
e. Why didn't the Division wait until the completion of the U.S. trials to issue an approvable letter?
f. Can you name another instance where a drug was issued an approvable letter before the U.S. clinical trials were complete? Can you name another instance where any division issued an approvable letter based on two foreign trials which were reprimanded by the FDA and information from an incomplete U.S. trial?
g. Is the fact that you characterized mifepristone as approvable – based on two faulty French trials, one incomplete U.S. trial, after only six months of consideration – evidence that there is a lower standard for women's health at the FDA, especially when the special interest of abortion is involved? If not, can you point to another example of a drug which was characterized as approvable after similarly slapdash consideration?

12. On July 18, 1996, the Executive Secretary of the FDA, Philip Corfman, hosted a dinner for the members of the Advisory Committee for Reproductive Health Drugs, which voted 6-0 (with two abstentions) for the drug's approval.

    a. Is dinner for the Committee, prior to its review of a drug and vote on its safety and effectiveness, part of standard FDA procedure for drug approval?
    b. Who paid for the dinner? Did the Population Council pay? Did the FDA pay? Please provide any relevant receipts.
    c. Who from the FDA attended the dinner?
    d. Who else attended the dinner?
    e. Did anyone from the Population Council attend the dinner?

f. Did anyone from the Clinton administration, outside the FDA, attend the dinner?
g. Was the approval of the drug discussed at the meeting?

13. In an interview with *Choice! Magazine* of Planned Parenthood[3] the following exchange took place between your colleague (the other witness requested by the Democrats for the May 17 hearing), Dr. Susan Wood, and a representative of Planned Parenthood:

    Planned Parenthood: Now that you've gone, who is left to advocate from inside the FDA?

    Wood: "Many good people at FDA are still there. The Office of Women's Health is still there. I hope it will be able to continue the good work it was able to do before. People in the review divisions are still there, not just in the reproductive division, but elsewhere."

    This statement names two divisions in which you worked during your career at the FDA.

    d. These statements are troubling, especially considering the forum. In your opinion, what type of "advocacy" is Planned Parenthood asking about? Abortion rights advocacy?
    e. If we are to believe that the FDA goes about the business of objectively investigating evidence for the safety and efficacy of drugs, what need is there for "advocacy" within the FDA?
    f. In your opinion, what sets the people in the reproductive division apart from the "people" referred to in this interview? Is it advocacy?
    g. Is recommending a drug as approvable after only six months of review and based on two faulty, non-controlled foreign trials and one incomplete U.S. trial, withholding the flaws of the pivotal studies from its Advisory Committee, assigning to it a Priority status, then announcing its approval to a list of women's advocacy groups a form of advocacy? Is the general "wait and see" attitude of the FDA in the face of the multitude of serious and fatal events, which appears to be inconsistent with the FDA's caution in other instances, another form of advocacy?

14. Is the climate at FDA such that it is more likely to disbelieve or seek to discredit science-based evidence of the dangers of reproductive health technologies, like the evidence which demonstrates that mifepristone may cause serious hemorrhage, infection, and death?

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[3] Laura Lambert, *Meet Dr. Susan Wood*, Nov. 23, 2005, available at http://www.plannedparenthood.org/news-articles-press/politics-policy-issues/birth-control-access-prevention/meet-dr-susan-wood.htm (last visited September 7, 2006).

Lisa D Rarick, MD
RAR Consulting, LLC
Reproductive Health and Regulatory Affairs
215 Midsummer Circle
Gaithersburg, MD 20878
301.548.9750
rarick215@comcast.net

September 19, 2006

Mark E Souder
Chairman
Subcommittee on Criminal Justice
Drug Policy and Human Resources
Congress of the United States
House of Representatives
Committee on Government Reform

Re: Subcommittee Hearing, "RU-486: Demonstrating a Low Standard for Women's Health?"

Thank you for the opportunity to respond to your letter dated September 13, 2006. I have reviewed the list of questions and provide the responses here. Thank you for including these responses in the written record.

1. The FDA makes the decision of maintaining approval or removing a drug from the market based on a risk/benefit assessment. Any risks found with the use of mifepristone are reviewed. New risk information is assessed as balanced by benefits. New risk information is added to labeling.

2. I was not present at the May 11, 2006 CDC conference.
a. I understand that some evidence may point to an effect of mifepristone on the immune system – but I am not aware that "consensus" exists on this point.
b. Among other things, this information needs to be corroborated in humans. The results in humans would allow more discussion of the impact or significance of any possible effects.

3. Are you aware of.... Answer: No Second part: Same answer as number 1. There is no specific number of transfusions that would result in withdrawal. Each case is considered and evaluated.

4.
a. Priority review is also assigned when no other drug is available for the indication. Other examples of drugs assigned "priority" review status for conditions that are not considered traditional "diseases" would be those that meet the requirements for "priority" designation in any area. Other examples of drug review in conditions not traditionally considered as "diseases" would include conditions such as infertility, desire for pregnancy prevention (contraception), erectile/sexual dysfunction, urinary frequency, urinary urgency, postmenopausal hot flushes, and premenstrual syndrome.
b. Subpart H and priority review are different designations. I would not agree that the subpart H designation had anything to do with the priority review designation.
c. Taking an action within 6 months does not mean that the drug must be approved in six months. As your question indicates, the initial review did meet the priority review timeframe and resulted in an "approvable" action letter. Several further cycles of review were employed prior to the issuance of an "approval" action letter. Once a sponsor receives an "approvable" letter it is required to submit a "complete response" to that letter which starts another review cycle (six month cycle no matter if initially a standard or priority designation). The complete response is reviewed by the agency (six months) and an action is taken (again with all three options possible—nonapproval, approvable, or approval).
d. The Division of Reproductive and Urologic Drug Products reviews applications as appropriate to this division. Priority review designation is made for products that meet the requirements for priority review (in this case, no other drug approved for the indication).
e. I am not familiar with the specific details of the user fee system so am unable to respond to this question.
f. I do not know the answer to this question, nor do I have any documents on this point.

5.
a. I do not recall the exact number of FTEs (full time equivalents) assigned to DRUDP. As you may be aware, the Division teams include members (chemists, statisticians, biopharmaceutics experts) who perform work within the Division but officially report to another Division.
b. I believe the FDA could provide you with the number of FTEs currently in the various review divisions.
c. No.
d.-f. I no longer have access to this information.

6. My comment was specifically that randomized, placebo-controlled trials were not reasonable for exploring drugs indicated for the termination of pregnancy. Comparing two methods of medical abortion is reasonable. Suggesting that women who want to terminate pregnancy enroll in a trial, in which half will be given placebo, is not logical. Natural history of pregnancy tells us that the vast majority of women who are pregnant will remain pregnant if given placebo. In the case of known natural history, trials can be performed without a concurrent comparison group as the protocol can call for a comparison to "historical controls." This is often the case in contraceptive trials and is a logical approach to pregnancy termination trials.

7.
a. I think this is a matter for discussion at the FDA. The negative consequences (reduced access, no alternative to surgical therapy, etc) would be considered along with the potential benefit.
b. I would need much more information about the nature of the "causal link" in order to consider this question.

8.
a. Again, this is a matter for discussion at/with the FDA.
b. I am not familiar with any examples where a drug was withdrawn while investigated.
c. Drugs are sometimes withdrawn based on associations—Vioxx and Baycol are examples.

9.
a. The review division accepted the filing of mifepristone based on the contents of the submission.
b. I don't recall if I was aware of involvement prior to my involvement in the drug review process (I was involved in the various cycles prior to actual approval).
c. I was not aware of any such communication during my involvement with the review of mifepristone.

10.
a. My understanding is that a form 483 is the inspectors' tool for providing comments to sponsors resulting from an inspection. Inspections can be of clinical trial sites as well as manufacturing sites. The FDA would have more specific information about the form and its uses.
b. I would need to see the referenced memo and medical officer review memos to answer this question.
c. I have no access to information or documentation on this point.
d. Form 483s provision is extremely common and serves as the Division of Scientific Investigations' primary method of providing sponsors with comments. The findings would have been conveyed to the FDA review team and considered in their review.
e. The form 483 reports that some documents could not be located. There is no mention in the quoted excerpt of whether the inspectors could not locate documents related to adverse events.
f. My understanding from the quotations provided is that some women were excluded from the study analysis because pregnancy tests were not performed. This is possible in clinical situations where pregnancy is obvious. It would not be expected that reports would be available for women who were excluded (as these women and their reports would not be part of the trial).
g. I believe the Division of Scientific Investigations would be in the best position to provide information to answer this question.

11.
a. The acceptance of foreign data is the subject of a CDER "Guidance to Industry" and provides answer to this question
b. The French trials were not considered "compromised."
c. The sponsor desired to perform a US trial.
d. and e. The US trial was not a requirement of the FDA.
f. The FDA has answered this question in the past, but I don't have immediate recall of the examples. I recommend asking the agency for this information.
g. Again, as the questions posed here seem rhetorical, I am unable to answer them. I can confirm, again, that the mifepristone application was held to the same high standard as any other NDA reviewed at the FDA.

12.
a. Dr. Corfman organized this event, and I do not recall attending. I do not believe that dinner is a requirement for Ad Com meetings.
b– f. I have no information on these points.
g. The general rule is that the Ad Com members are not to discuss the Ad Com topic at social events (dinner, lunch at meeting, etc). Since I was not there, I have no specific evidence one way or the other.

13
d. I believe the FDA's Office of Women's Health contains as part of its mission to serve as a "champion for womens' health" which includes serving as an "advocate" for improved women's health (as relates to regulated products).
e. I believe the intent of this "advocacy" is to provide oversight regarding inclusion of women in clinical trials, oversee high priority projects for improvement in womens' health as related to FDA-regulated products and to provide access for concerned women and organizations to dialogue with the FDA.
f. As I was not part of the interview you quote, I cannot comment on what meaning either individual ascribes to any word or phrase.
g. As per 11g.--this NDA was held to the same high standard as any other NDA reviewed at FDA.

14. The climate at FDA is one of concerned, dedicated public health scientists and staff who consider their mission, calling and serious responsibility to be the protection and promotion of public health.

THE GEORGE
WASHINGTON
UNIVERSITY
MEDICAL CENTER
WASHINGTON DC

DEPARTMENT OF ENVIRONMENTAL AND OCCUPATIONAL HEALTH
SCHOOL OF PUBLIC HEALTH AND HEALTH SCIENCES

October 13, 2006

The Honorable Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
  Drug Policy, and Human Resources
House of Representatives
Washington, DC 20510

Dear Mr. Chairman,

Thank you for the opportunity to follow up on the May 17, 2006 hearing entitled "RU-486: Demonstrating a Low Standard for Women's Health?" held before the Subcommittee on Criminal Justice, Drug Policy and Human Resources of the House Committee on Government Reform. I include with this letter my responses to the 12 questions for the record that you sent on September 6, 2006. I respectfully request that my responses and corresponding attachments be entered into the record for this hearing.

Sincerely,

Susan F. Wood, PhD
Research Professor
George Washington University
School of Public Health and Health Services
The Project on Scientific Knowledge and Public Policy

THE PROJECT ON SCIENTIFIC KNOWLEDGE AND PUBLIC POLICY
2100 M STREET, NW • SUITE 203 • WASHINGTON, DC 20037 • 202-994-0774 • FAX 202-994-0011
WWW.DEFENDINGSCIENCE.ORG

1. In evaluating the benefits and risks of any medical product or procedure, FDA should examine all relevant data to assess whether a product should be approved, under what conditions and restrictions, what information needs to be available to health professionals and patients, and whether overall benefits outweigh the risks. Any identified risk is of concern and should be investigated appropriately. FDA has identified 5 deaths due to sepsis after a medical abortion which is approximate mortality rate of 1 in 100,000 uses. The response by FDA in working with CDC and NIH to carry out needed research, as well as providing important information to health professionals providing medical abortion and follow-up care is an appropriate response at this time.

2. The objectives of the May 11, 2006 meeting, the Emerging Clostridial Disease Workshop, as stated in their final agenda were as follows:

   > "Our goal of this public workshop is to identify research needs and priorities that will enable rapid progress in understanding the virulence, pathogenesis, host factors and nonantimicrobial risk factors contributing to reports of morbidity and mortality associated with Clostridium sordellii (C. sordellii) and Clostridium difficile (C. difficile) .
   >
   > The outcome of this workshop will be a draft research agenda that also provides recommendations for detecting cases and conducting surveillance of diseases and organisms."

   This meeting was not designed to reach a consensus on the mechanism of action, but rather was gathering together a range of researchers and clinicians to assess the research needs. I disagree with your assertion that I oppose a consensus reached by the workshop. The research priorities identified demonstrate that from basic science to case reporting to better surveillance of pregnancy related mortality are all necessary to understand the deaths associated with C sordellii including those associated with mifepristone. I concur with the need for this research and surveillance and urge that this research be a priority for FDA, CDC and NIH. I attach the Summary of Proceedings (Attachment 1).

3. Based on FDA analysis, the current US transfusion rate associated with the use of mifepristone is 0.035%. This is lower than the rate seen in the clinical trials submitted for product approval (rates of 0.15% and 0.2%). The transfusion rate for medical abortion is therefore not more than expected.

4. Medical abortion provides an early and non surgical method for terminating a pregnancy. This option provides a method for women who do not wish to undergo surgery and anesthesia or for whom surgery is not medically appropriate. They may also prefer the abortion be more private. Research by Harvey et al. (Family Planning Perspectives, 33:5, 212-216, 2001, Attachment

2) measure the satisfaction by US women choosing between medical and surgical abortion and identify the factors that are associated with preferring either medical or surgical abortion.

FDA has provided information that it is relatively uncommon for drugs to be withdrawn from the market while manufacturers investigate severe adverse reactions. In my experience, I was at FDA at the time that Lotronex was voluntarily withdrawn from the market by the manufacturer and then returned under more restricted distribution.

I am not aware of any drugs that have been withdrawn for safety reasons that were based solely on an association with adverse events.

5. It is my understanding that FDA does not concur that the numbers of deaths you identify are due to a direct drug effect of mifepristone. Regardless, withdrawal of this FDA approved method of medical abortion would remove a safe and early medical method for women terminating a pregnancy. Based on current knowledge, I would not support withdrawal of mifepristone from the market.

6. In my testimony and based on my reading of the presentations and recommendations of the CDC workshop, I call for increased research in the possible impacts of mifepristone on the immune system, the nature of the infections and human response to infection by C. sordellii and its connection to termination of pregnancy, whether through medical abortion, miscarriage or delivery. The workshop participants including the scientists and clinicians whom you identified delineate a wide range of research needs in order to address the deaths due to C. sordellii. I do not question the particular studies cited, and the hypotheses put forward are worth further investigation.

   My testimony does not rule out a possible impact of mifepristone on the immune system, but questions whether there is adequate evidence to link any impact on the immune system to the infections by C. sordellii and the deaths due to this infection. My testimony calls for additional research in all of these areas, to begin to establish any identifiable risk factors to help prevent and treat infection from C. sordellii.

7. The mission of the FDA Office of Women's Health is to be the "champion for women's health, inside and outside the Agency" (Attachment 3). It has served in this role since its creation in 1994 and I express my continued hope that it will still be able to advocate for good science and good decision making to promote the health of all women.

   I believe that the vase majority of the scientific and professional staff at the FDA are committed to ensuring that the best available evidence is was underlies FDA decisions and are committed to the public health mission of the Agency.

The review of mifepristone took place prior to my tenure at the FDA, however the total review and approval time took up to 54 months rather than the 6 months you identify. The FDA Office of Women's Health routinely announces information about FDA actions that effect women to women's health organizations, health professional organizations, and other non-government organizations interested in women's health. Any announcement by FDA OWH would have been part of this routine outreach. FDA has been rigorous in its tracking of adverse events due to the requirements that all healthcare providers who wish to prescribe mifepristone must report all adverse events, and has evaluated and responded to that information appropriately.

8. My concern is always that good scientific and medical evidence drive the decisions made by the FDA. Unfortunately, that was not the case with the Plan B decisions which disregarded the strong agreements and recommendations by multiple levels of the scientific professional staff at FDA. See attached GAO report regarding the May 2004 initial denial of OTC status of emergency contraception and my perspective article in the New England Journal of Medicine from October 2005 (Attachments 4 and 5).

In the case of mifepristone, the FDA scientific staff is continually evaluating the evidence and the actions taken by the Agency reflect the best available evidence and the recommendations of the scientific and medical staff.
Women's health is perhaps at higher risk of intervention from outside of the Agency for reasons that are not based on the scientific and medical evidence, and I urge that FDA be allowed to make its decisions independently and based on the best available evidence as evaluated by the scientific staff.

9.

My current position is that of Research Professor, George Washington University School of Public Health and Health Services, working as part of the Scientific Knowledge and Public Policy Project since July 2006. I have worked with a number of non-profit organizations as an advisor or consultant since my resignation including RHTP and have done so quite publicly. Indeed on my Op-Ed piece in the Washington Post (March 1, 2006, Attachment 6) I am identified as a senior policy advisor to the Reproductive Health Technologies. However for several reasons, I do not believe it was relevant to my testimony on May 17 before the Subcommittee. By the time of the hearing, or even at the time I was invited to the hearing, I was no longer employed as senior policy advisor by RHTP. My work with them had been limited to a 6 month period between Nov. 1 and May 1 2006, and was focused on speaking around the country about the importance of using science in health policy decision-making specifically in the case of Plan B emergency contraception. The major message I was delivering was about good scientific evidence, proper FDA procedure, and the fact that access to emergency contraception for women over the age of 17 has the potential to reduce unintended pregnancies and the need for abortion, something I think we all agree on. At the time I was or had been a consultant for RHTP, as well as for other organizations including WomenHeart, the National Center for Research on Women and Families, and the Union of Concerned Scientists. I was also an Adjunct Associate Professor at the American University School of Government. I also was a member of the board of Women's Policy, Inc a non-partisan organization. I had also done one-time limited consulting jobs for several pharmaceutical companies.

During my time traveling and speaking on "Women's Health, Emergency Contraception and the FDA" (my usual title) I spoke to a wide range of organizations. These were based on invitations that came in after my resignation. I gave presentations to a number of women's organizations, family planning and pro-choice organizations, and health professional organizations, but that is only part of the story. By that time I was also invited to give academic presentations to: Bowdoin College, Boston University School of Medicine, Drake University, Duke University, Emory University, Harvard University School of Medicine, Iowa State University, Princeton University, Stanford University School of Medicine, UCLA School of Public Health and School of Medicine, UCSF School of Medicine, University of Idaho, University of Illinois at Chicago, University of Michigan, University of New Hampshire, University of Washington, University of Wisconsin, Wake Forest University School of Medicine, and Washington University School of Medicine and School of Law, among others.

As I was invited to testify due to my former position at FDA as Assistant Commissioner of Women's Health and former Director of the Office of Women's Health, as well as my years of additional experience within government, I didn't feel it was necessary to include all of this very public information in my testimony.

I am trained as a biologist, with specific training in cell biology with a PhD from Boston University with additional training and research experience in neuroscience at the Johns Hopkins University School of Medicine. The primary point of my testimony was and remains that more research is critically needed both in the area of the potential effect of mifepristone on the immune system in both animal and human models, as well as in improving research and surveillance on maternal mortality due to C. sordellii infection and other causes of maternal mortality and morbidity.

Speaking and giving lectures, as well as giving testimony upon request by Congress, is consistent with my commitment to working with our science based agencies, the medical and research communities, policymakers and those who advocate for women's health to provide information, carry out research and promote the health of women and men.

10.

The CDC workshop speakers and participants discussed the need for further surveillance of maternal mortality to better evaluate the relationship between C. sordellii infection with pregnancy. Research initiatives into both maternal deaths due to C. sordellii and deaths after medical abortion due to C. sordellii are needed if we are to prevent and/or effectively treat this rare infection. This responsibility does not lie solely with FDA but also with our other research and prevention agencies, the NIH and the CDC.

Broadening the research agenda to address the health of all women who may be at risk of this rare infection is not deflecting the blame but rather following the evidence in all relevant directions with the goal of preventing or treating C. sordellii infection.
The Mission of the Reproductive Health Technologies Project is as follows (Attachment 7):
"The mission of the Reproductive Health Technologies Project is to advance the ability of every woman of any age to achieve full reproductive freedom with access to the safest, most effective, appropriate and acceptable technologies for ensuring her own health and controlling her fertility. To fulfill this mission, we seek to build consensus in support of an education, research and advocacy agenda for reproductive health and reproductive freedom. We seek consensus through a process of dialogue among diverse communities about technological developments and their global implications."

The Reproductive Health Technologies Project along with other women's health and health care organizations sent an open letter to the CDC workshop members expressing their commitment to working with the research community and the Federal Agencies to address the emerging health risks due to C. sordellii. In part they state:

"Like you, women's health experts and advocates across the country are concerned by the deaths of four women from Clostridium Sordellii following medical abortion. According to reports from the CDC, we understand this is part of a larger pattern of fatal infection among obstetric and gynecologic patients....We are hopeful that the technical expertise and resources represented by the convening agencies will be used to investigate the underlying pathology of these infections and evaluate different options for care...The signatories to this letter also want to express our commitment and willingness to work with public health professionals at a national and local level to better determine options for prevention and treatment in emerging clostridial infection, particularly as it relates to obstetric and gynecologic care." See full letter, (Attachment 8).

11. Mifepristone was approved with additional restrictions upon the manufacturer and health care providers. Unlike other products, health care providers are required to report any serious events to the manufacturer, who then reports this to the FDA. The adverse event reports to the FDA are therefore far more complete than would be known through the usual Adverse Event Reporting System.

12. Reports concerning infection in women following medical abortion with mifepristone should be evaluated along with other information including data from better surveillance of maternal infection, and further in vitro and in vivo studies to assess the impact of mifepristone on the immune system as well as the relationship of the end of pregnancy with risk of C. sordellii and other infections.

Mark E. Souder
Chairman
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
Congress of the United States
2157 Rayburn House Office Building
Washington, D.C. 20515-6143

Dear Chairman Souder,

Thank you for your patience while completed my answers to the questions that you sent me. I have reproduced your questions in BLACK, and my answers in BLUE. I have also attached the following supporting documents which you should have received with this email communication:

1. American College of Obstetrics and Gynecology Practice Bulletin Number 67, October 2005 entitled **Medical Management of Abortion.**

2. **Abortion Reporting in the United States:**
An Examination of the Federal-State Partnership
By Rebekah Saul
Family Planning Perspectives
Volume 30, Number 5, September/October 1998

3. Letter from Mr. Walter Weber to Tommy Thompson, Secretary, Dept of Health and Human Services
4. Reply to Weber letter from Julie Gerberding, Director Center for Disease Control

5. **Fatal Toxic Shock Syndrome Associated with *Clostridium sordellii* after Medical Abortion**
Marc Fischer, M.D., M.P.H., Julu Bhatnagar, Ph.D., Jeannette Guarner, M.D.,
Sarah Reagan, M.P.H., Jill K. Hacker, Ph.D., Sharon H. Van Meter, M.D.,
Vadims Poukens, M.D., David B. Whiteman, M.D., Anthony Iton, M.D., J.D., M.P.H.,
Michele Cheung, M.D., M.P.H., David E. Dassey, M.D., M.P.H.,
Wun-Ju Shieh, M.D., Ph.D., and Sherif R. Zaki, M.D., Ph.D.
From the Centers for Disease Control and
Prevention, Atlanta (M.F., J.B., J.G., S.R.,
W.-J.S., S.R.Z.); the California Emerging
Infections Program, Richmond (J.K.H.);
the Alameda County Coroners Office
(S.H.V.M.) and Health Department (A.I.),
Oakland, Calif.; the Department of the
Coroner (V.P., D.B.W.) and the Department
of Health Services (D.E.D.), Los Angeles;

and the Orange County Health Care
Agency, Santa Clara, Calif. (M.C.).
n engl j med 353;22 www.nejm.org december 1, 2005

6.. Pregnancy Related Mortality Surveillance U.S. 1991-1999. Morbidity and Mortality Weekly Reports (MMWR) Surveillance Summaries Feb 21, 2003/ 52 (SS02); 1-8. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5202a1.htm

7. **EARLY PREGNANCY TERMINATION WITH MIFEPRISTONE AND MISOPROSTOL IN THE UNITED STATES** IRVING M. SPITZ, M.D., D.SC., C. WAYNE BARDIN, M.D., LAURI BENTON, M.D.,AND ANN ROBBINS PH.D.
(N Engl J Med 1998;338:1241-7.)

Questions and Answers:

1. Those who attended the CDC conference on May 11th, "Emerging Clostridial Disease" seem to have reached a consensus in that there is clearly a mechanism by which mifepristone interferes with the immune response, and that there is an association between the use of Mifeprex and infection with C. Sordelllii, which FDA has acknowledged has killed five women(reported) thus far.

a. How does the medical community go about establishing a causal relationship? A causal relationship is based on the known facts in each individual case and the logical relationship between those known facts and established physiological processes. I will illustrate with an example from death certificates. In a death certificate, a medical personnel is asked to complete a document with a legal definition the "cause of death". This "cause of death" is recognized to be a chain of events which culminates in a death, as illustrated by the sections on the death certificate that the physician is required to fill out. In the case of a woman who dies from heart failure, for instance, the certificate will state:

Cause of death: heart failure

as a consequence of : cardiomyopathy

as a consequence of : ischemic heart disease

as a consequence of : hyperlipidemia.

And in Michigan, an question must also be filled out: Did tobacco contribute to the death Y N.

Thus, what actually killed the woman was high cholesterol which resulted in ischemic heart disease, which then resulted in her heart malfunctioning and this malfunction was eventually bad enough to kill her.

So there is recognition of a "chain of causality" inherent in the public health documents that interface between medicine and the legal community. And the term "cause" is taken at its face value to mean a link in that chain of causality. A cause is based on the known facts in each individual case and the logical relationship of different known and established physiological processes.

Is it proper to infer a causal relationship for C. Sordellii infection from the data available to us?

Now back to the question of causal relationship in the case of the young women who died of Clostridium Sordellii sepsis after taking mifepristone. Young women are not known to die frequently of any cause, let alone the cause assigned by a physician/coroner in these cases. The examining coroner/physician looks at the unique circumstances of that individual case and puts together a logical sequence of pathophysiological events that match the findings of the clinical recoord and the autopsy. In this instance, the coronors in California have done what any other physician does in completing the death certificate: they assigned a chain of causal links.

In the instances of these women, it was clear that:

1) the individual(s) died of systemic inflammatory response syndrome (i.e. sepsis).

2) It is clear from the autopsy and clinical records that no other know cause of this phenomenon was found except the presence of clostridium sordellii in the endometrium.

3) It is established, as discussed in the CDC meeting in Atlanta, that clostridium sordellii can cause sepsis by producing lethal toxin.

4) It was also demonstrated at the CDC meeting in Atlanta, that mifepristone can interfere with the cellular immune response to Clostridial lethal toxin, rendering an organism more succeptible to effects of Clostridial lethal toxin.

5) It is clear from the individual(s) medical records that each of these women were exposed to mifepristone days before dying of sepsis.

6) In the absence of any medical literature anywhere which supports Clostridium sordelli sepsis or lethal toxin induced sepsis occurring in a pregnant woman with a live fetus, it is clear from the clinical record that such a phenomenon would not have happened had an abortion not been undertaken.

Thus, it is a straightforward matter to assign the cause of sepsis to mifepristone, and the California physician coroners did not hesitate to assign the cause of death to mifepristone.

What other data is needed? No other data is needed to infer a causal relationship between death from C. sordellii sepsis and mifepristone.

Postmarketing studies, which had been required by the FDA at the time of approval of mifepristone, but which have never been completed, would serve to delineate the statistical frequency of death from C. sordellii sepsis. From the estimates so far that can be made one can estimate that at least one woman in every 100,000 mifepristone abortions will die from C. sordellii sepsis.

b. Do you recommend leaving Mifeprex on the market while investigations into a causal relationship between Mifeprex and serious adverse events move forward? No. To continue to allow women to be exposed to a drug with at least a 1 in 100,000 chance of death from sepsis, when the alternative, surgical abortion, results in an estimated rate of death which is ten times less, is irresponsible.

Furthermore, the risks of hemorrhage during mifepristone abortions are estimated to be ten to a hundred fold higher than during surgical abortions. In the U.S. clinical trial by Spitz 2.6% of women required emergency surgery for hemorrhage, which means that of every 100,000 mifepristone abortions, 2,600 women will require emergency surgery for severe bleeding. Spitz also found that 200 women of every 100,000 abortions will require transfusions. Recall also that these numbers were generated under the best clinical circumstances of a clinical trial, with women being carefully followed for complications.

Further, Jensen, one of the priciple investigators during the U.S. clinica trial, compared surgical abortion complications to medical abortion complications and found 12.5% underwent emergency surgery for acute bleeding. This means that at his site, 12.5 out of every hundred women had to have emergency surgery for hemorrhaging. In constrast when he examined the results of the surgical abortion patients, *No* women in the surgical group required emergency surgery for acute bleeding.

These numbers have been grossly reflected in the Adverse Event reports already submitted to the FDA. Further delay in withdrawal of this drug will only result in further excess deaths and transfusions at a predictable rate, all preventable.

Since the failure rate of mifepristone is between 8 and 25% depending on the gestational age at which it is administered, no patient should be offered mifepristone without access to services for surgical completion. This means that women who are offered mifepristone should by definition have access to surgical services which are by far less dangerous.
There is no reason to leave mifepristone on the market any longer.

c. Is it common for the medical community to be as cautious as the FDA and Danco have been in the case of Mifeprex in inferring a causal relationship for data which seem to clearly indicate one?

It is not common for a pharmaceutical to exercise as little caution as has Danco and the FDA in the case of mifepristone associated adverse events. FDA and Danco have been irresponsible in their treatment of the Adverse Events associated with Mifeprex use.

The entire purpose of requiring 2 controlled randomized trials prior to approval of a drug is to be able to delineate the safety and efficacy of a drug while minimizing the inherent bias of the investigators. Those studies are supposed to be designed beforehand with a certain statistical power for determining the frequency of adverse events. Pharmaceutical companies delineate, before the trial is even performed, what number and nature of adverse events will result in no longer pursuing the development of the drug. And when that number is reached, the development of the drug is discontinued, or the drug is withdrawn from the market voluntarily. This has been illustrated by the fact that FDA has not had to forcibly withdraw a drug from the market for the past 20 years, the drugs have voluntarily been withdrawn by responsible drug companies in the best interests of their patients.

In contrast, the lack of any controlled or randomized trial design in the single U.S. clinical trial (the data of which was not even presented to the FDA Advisory Committee before asking for their vote) prompted the Statistical Reviewer for the FDA to comment in the NDA documents that it was purely a matter of clinical judgement whether or not RU486 showed any meaningful therapeutic benefit when compared to surgical abortion. Contrast this comment with the usual detailed statistical analysis given any other drug in any other NDA of your choice.

Since in fact a drug approved under Subpart H must show meaningful therapeutic benefit over standard care, then the approval process itself showed a cavalier disinterest in the actual scientific merits of the drug. Since the lack of any meaningful therapeutic benefit did not hinder the drug approval process, one might conclude that the FDA had decided that mifepristone was going to be approved, regardless of what the data actually revealed.

This same attitude seems to prevail currently with both Danco and the FDA. When asked how many deaths, or how many transfusions would constitute grounds for withdrawal of approval, the answer from FDA officials was non-committal, implying that neither the FDA nor Danco has done any statistical analysis to determine when the risk to American women outweighs the benefit obtained from availability of medical abortion with mifepristone. This is highly irresponsible, and argues for the opinion that regardless of the number of deaths or injuries resulting from this drug, Danco and the FDA are "ideologically committed" to keeping this drug available. This ideological committment at the cost of a ten fold increase in mortality from sepsis, and increase in necessity for emergent surgical intervention, and increase in necessity for blood transfusions, is in direct conflict with the stated purpose of the FDA, which is to safeguard the health of the American people.

Further, the reluctance of the FDA and Danco to acknowlege the role of mifepristone in what is clearly a causal chain of events in the deaths of the(at least) 5 women from Clostridium sordellii sepsis borders on a purposeful ignorance. This appears to be stemming from an ideological committment to keep mifepristone on the market, which cannot allow for objective analysis of data. The clear financial motivation for Danco to refuse to acknowlege the causal link and take the appropriate action of withdrawing mifepristone is self evident.

2. The FDA has acknowledged the deaths of eight women, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection have been associated witht he use of Mifeprex thus far. In light of this information, the prudent course of action would seem to be pulling the drug off the market while an investigation into the dangerous properties of this drug proceeds. In your opinon, what harm would come to women if this drug was pulled from the market during an investigation into Mifeprex's relationship to C. Sordellii infection?

Examination of the American College of Obstetrics and Gynecology Practice Bulletin Number 67, October 2005 entitled Medical Management of Abortion, gives the recommended criteria under which medical abortion services are to be provided. Page 8 contains the following statements:

"Because teratogenicity of medical abortifacients becomes an important issue if the pregnancy continues, patients must be informed of the need for a surgical abortion in the event of a failed abortion."

and also on Page 8:

"Surgical curettage must be available on a 24 hour basis for cases of hemorrhage..."

Thus it is clear that women who undergo medical abortion must have the option of surgical abortion services available to them.

Since these women have the option of surgical abortion services available to them prior to undertaking a medical abortion procedure, then there is nothing that would prevent the woman from obtaining a surgical rather than a medical abortion.

Since the risks of death from sepsis, hemorrhage, and transfusion are substantially less with surgical abortion than with medical abortion, then there is no detriment to women from withdrawing approval of mifepristone and no longer providing this more dangerous option.

In brief, no harm would come from withdrawing mifepristone, and in fact, a net benefit of decreased numbers of deaths and infections and hemorrhages and transfusions related to abortion would result if mifepristone were no longer available in the U.S.

3. In your testimony, you claim death from C. Sordellii is over 50 times more common in chemical abortion than it is in childbirth. Proposnents of the drug have suggested that the higher reported incidence of death is a symptom of the tight reporting requirements for the use of RU-486, rather than its higher incidence in patients who have had a chemical abortion. What is your response to that?

Since death in pregnant women who has delivered is accompanied by a death certificate, it is highly unlikely that there are women who die during childbearing, whose death is not documented, and the causal event determined. In many states, maternal deaths are followed by an obligatory coroner's investigation. The number of maternal deaths is tracked by state and federal organizations as well as by hospital review committees, insurance companies, malpractice companies, pediatric and obstetrical organizations and other medical organizations. Attached also is a letter from Dr Gerberding, Director of the Center for Disease Control in response to questions about the validity of statistics in regard to maternal mortality and abortion-related mortality. She states at 2. " The live birth component of the pregnancy estimates (of maternal mortality) is highly reliable".

It would be fantastically improbable that a disease like Clostridium sordellii, known in the medical literature, and with a very unique presentation, could account for the deaths of 1 in 100,000 women who give birth, and this be unreported. Proponents who say that the difference between the rate of death from C. sordellii in childbirth as compared to medical abortion are postulating that 1 in 100,000 women who have children every year die of C. sordellii. So, in other words, they are claiming that there were 357 deaths from C. sordellii in pregnant women from 1991-1999. I would like to see the data which supports this preposterous claim.

Since the clinical syndrome associated with C. sordellii sepsis is so unique and dramatic, and since all deaths of women in childbearing are followed by numerous investigative agencies, one would be hard pressed to provide evidence that there are a substantial number of maternal deaths from C. sordellii which go unreported or unrecognized. And the CDC itself, which has access to all of the national data, found a total of 8 cases of death from C. sordellii in all pregnancies from 1977 to 2001 ie in 24 years of childbearing statistics.

In contrast, the reporting of abortion related complications is voluntary, incomplete and often inaccurate, as stated in the recent article by Saul (See attached), and as confirmed by Dr. Gerberding Director of the CDC in her letter addressing questions about the collection of data on mortality related to abortions (also attached) where she states

" Estimates of all abortions are based on CDC's abortion surveillance system, which relies on state abortion reporting systems."

(Saul details the brokenness of the state abortion reporting systems, many of which are voluntary, and several states submit no data whatsoever on abortions to the CDC.)

Gerberding goes on to state " The nature of the surveillance systems make it difficult to obtain complete data. The PMSS (ie Pregnancy Mortality Surveillance System) compiles data from 50 states, the District of Columbia, and New York City. Abortion surveillance involves data from 47 states, District of Columbia and New York City. These systems are voluntary, (CDC does not provide renumeration for data) and rely primarily on death certificate data which may or may not provide information that the death was maternal or abortion-related."

Further, the connection between a death from C. sordellii infection and mifepristone abortion is often missed, as evidenced by the fact that 3 of the deaths reported after mifepristone use were not even recognized as being caused by C. sordellii until the CDC investigation was undertaken.

More inaccuracy in reporting deaths and other severe adverse events related to mifepristone occurs from fact that a significant percentage of women who present to the emergency room with complications do not reveal to the emergency room doctor that they have taken mifepristone. Since these ER doctors will not have access to the patients records from the abortion clinic, the complication will not be recognized or reported as being related to mifepristone use.

4. When women begin to succomb to C. Sordellii infection, it presents like a miscarriag, if it presents with any symptoms at all. In terms of what symptoms and conditions indicate infection by C. Sordellii, does the California investigation mandated by the CDC properly take into account the unique properties of this diease? Is there anything else that the CDC could look for that would improve the study?

I do not have access to the details of the study design being undertaken in California. However, it is clear that if a serious investigation is to be undertaken to determine rates of infections, deaths, hemorrhages and other adverse events related to mifepristone use, and in comparison to rates of these associated with surgical abortion, then there must be a mechanism to identify and compare women who have surgical vs mifepristone abortion, and to follow these women for complications. See study by Saul attached.

5. Since approval according to Subpart H guidelines requires a clinical benefit over existing treatments, should the FDA have required a concurrent trial comparing the safety and effectiveness of first-trimester surgical abortion vs. mifepristone-misoprostol chemical abortions?

Yes, according to ICH-GCP guidelines a randomized controlled trial is the only way to eliminate inherent bias in the study. The FDA was required by it's own documents to require 2 randomized controlled trials as a basis for the NDA.

As I addressed this above, the lack of any controlled or randomized trial design in the single U.S. clinical trial (the data of which was not even presented to the FDA Advisory Committee before asking for their vote) prompted the Statistical Reviewer for the FDA to comment in the NDA documents that it was purely a matter of clinical judgement whether or not RU486 showed any meaningful therapeutic benefit when compared to surgical abortion. Contrast this comment with the usual detailed statistical analysis given any other drug in any other NDA of your choice.

Since in fact a drug approved under Subpart H must show meaningful therapeutic benefit over standard care, then the approval process itself showed a cavalier disinterest in the actual scientific merits of the drug. Since the lack of any meaningful therapeutic benefit did not hinder the drug approval process, one might conclude that the FDA had decided that mifepristone was going to be approved, regardless of what the data actually revealed.

Do any such studies exist?

The following studies all incorporate the study design of a randomized controlled trial in the setting of medical abortion:

Creinin MD, Vittinghoff E."Methotrexate and misoprostol v. misoprostol alone for early abortion: A randomized controlled trial" JAMA 1994 272:1190-5.

Jain JK, Dutton C, Harwood B, Meckstroth KR, Mishell DR, Jr. "A prospective randomized double blinded placebo-controlled trial comparing mifepristone and vaginal misoprostol with vaginal misoprostol alone for elective termination of early pregnancy" Human Reproduction 2002; 17: 1477-82.

Bartley J, Brown A, Elton R, Baird DT. "Double blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion up to 63 days gestation" Human Reproduction 2001;16: 2098-102.

These are well known studies, and the design of a randomized controlled trial could have easily been performed in the setting of comparing medical vs surgical abortion, since all of the trial participants agreed to have surgical abortion performed in the event of a failure of the medical abortion.

What were the results?

The only study which compared the results of surgical abortion with mifepristone-misoprostol abortions using the patients from the U.S. clinical trial and comparing them with other surgical abortion patients was the study by Jensen (one of the principle investigators in the single U.S. clinical trial).

Jensen JT, Astley SJ, Morgan E, NicholsMD, " Outcomes of suction curettage and mifepristone abortions in the United States: a prospective comparison study" Contraception 1999; 59:153-159

Dr. Jeffrey Jensen compared 178 patients who underwent mifepristone/misoprostol abortions with 199 patients who later received surgical abortions at the same clinical site. The primary procedure failed (*i.e.*, there was a subsequent surgical intervention) in 18.3 percent of the mifepristone-misoprostol patients and 4.7 percent of the surgical patients. Of the mifepristone-misoprostol patients who failed their primary procedure, 12.5 percent required surgical intervention for acute bleeding, 43.8 percent for persistent bleeding, 15.6 percent for incomplete abortion, and 28.1 percent for ongoing pregnancy. By contrast, persistent bleeding was the sole cause for surgical intervention among the surgical abortion patients whose primary procedure failed.[13] In addition, mifepristonemisoprostol patients "reported significantly longer bleeding" and "significantly higher levels of pain . . . , nausea . . . , vomiting . . . , and diarrhea" than their surgical counterparts.

There was clearly no therapeutic advantage demonstrated for mifepristone abortions as compared to surgical abortions in this paper, which is the only published report comparing the U.S. clinical trial participants with surgical abortion. In fact, mifepristone abortions failed more often, had more subsequent bleeding for a longer duration of time, had more emergency surgical intervention and were more painful than surgical abortions.

6. Although clinical trials for RU-486 occurred in controlled clinical settings, it is now the practice of many abortionists to instruct women to administer misoprostol at home. In light of the significant risk of infection, hemorrhage, and other adverse events, is this prudent?

No, it is clearly not prudent, nor were these regimens ever evaluated by the FDA for safety and efficacy. In fact, it is clear from FDA documents that the intent of approval of mifepristone as an abortifacient under Subpart H was to allay the concerns of those present at the advisory committee and within the FDA who were concerned about the unrestrained use of this drug, and it's potential for serious harm to women. Subpart H is the only mechanism by which the FDA could possibly apply post-marketing restrictions. FDA made clear to Danco that failure to comply with postmarketing restrictions could result in withdrawal of approval of this drug.

The 2000 Mifepristone Approvable Letter sent from the FDA to Danco/Population Council, stated that FDA had "considered this application under the restricted distribution regulations contained in 21 CFR314.500 (Subpart H) and concluded that restrictions as per [21] CFR 314.520 on the distribution and use of mifepristone are needed to ensure safe use of this product". According to the FDA's own rules regarding Subpart H in 21 CFR 314.520 " FDA may approve a treatment subject to special distribution or use restrictions that address outstanding safety issues". FDA uses Subpart H to place postmarketing restrictions on the use of a drug when FDA is concerned that "some drugs, however, are so inherently toxic or otherwise potentially harmful that it is difficult to justify their unrestricted use." FDA was willing " to approve such high risk drugs for early marketing if the agency can be assured that postmarketing restrictions will be in place to balance the known safety concerns." Postmarketing restrictions would be designed "to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restrictions".

Yet, in the case of mifepristone, these restrictions have been completely thwarted, and the FDA has taken no action.

On September 28, 2000, FDA approved mifepristone for termination of pregnancies up to 49 days gestation, under Subpart H, which FDA explained (in the Approval Letter to Sandra Arnold) "applies when FDA concludes that a drug product shown to be effective can safely be used only if distribution and use is restricted, such as to certain physicians with certain skills or experience." The FDA specifically approved a regimen that required the following: (available at http://www.fda.gov/cder/foi/label/2000/20687lbl.pdf)

First visit: "Day One: Mifeprex Administration" the patient reads the medication guide, signs the Patient Agreement and ingests 600 mg of mifepristone;

Second visit: "Day Three: Misoprostol Administration" the patient ingests 400 mcg of misoprostol orally unless abortion has occurred and been confirmed by clinical examination or ultrasonographic scan, and

Third visit: on or around "Day Fourteen: Post-treatment Examination" the patient returns to the practitioner for verification through a clinical examination or ultrasound that the pregnancy has been successfully terminated.

Planned Parenthood, the single largest provider of mifepristone abortions in the nation, does not adhere to the FDA approved regimen, and openly endorses publically a regimen that differs from that approved by the FDA.

Multiple abortion provider websites openly advertise abortions to 63 days gestation, or regimens including the vaginal administration of misoprostol, skipping the second office visit, which was designed for the safety of the patient, and early identification of difficulties in the abortion procedure, and different doses of mifepristone and misoprostol, none of which were studied or approved by the FDA. Even the Medical Director of Danco openly advertised on his website regimens of administration of mifepristone and misoprostol which differed from the FDA approved regimen.

The FDA also outlined in the Approval Letter two Phase IV study commitments (Post marketing Study committments):

1) "A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention." and

2)" A surveillance study on outcomes of ongoing pregnancies".

FDA also stated that "previous study questions related to age, smoking and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms"

Danco/Population Council have fulfilled none of these study requirements. Yet, FDA has taken no action, even though the FDA is authorized to withdraw approval if these postmarketing restrictions are not met.

Refusing to fulfill the postmarketing research studies, and changing the doses of mifepristone and misoprostol, and the conditions under which they have been administered has effectively led to a situation where the true safety of the currently used regimens have never been methodically studied, or examined in any unbiased fashion.

Further, over 90% of the AER's reported to the FDA were from women who were given a regimen which differed from the FDA regimen. 100% of the U.S. women who have died have had a regimen which differed from the FDA regimen. So, currently we have the completely unrestricted use of a drug which the FDA rightly recognized to be "so inherently toxic or otherwise potentially harmful that it is difficult to justify their unrestricted use." and for whom restrictions were applied at approval "to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restrictions".

Would you recommend FDA taking steps to prevent this practice, and why?

In light of the known dangers of the current unrestricted use of mifepristone and misoprostol, and the inability to enforce any of the postmarketing restrictions that might have limited some of the dangers of the approved FDA regimen, it is clear that the FDA needs to withdraw approval of mifepristone for use as an abortifacient.

7. Other panelists at the Subcommitee hearing, and Mifeprex labelling both suggest that infection and hemorrhage are the expected complications of chemical, surgical and spontaneous abortion. Some proponents of chemical abortion claim that chemical abortion is safer than carrying a pregnancy to term. Are these assertions true?

Chemical, surgical and spontaneous abortions all carry a risk of infection and hemorrhage. The question is the amount of risk associated with each of these procedures. Attached find an interesting correspondence between Weber and Dr. Gerberding, Director of the CDC regarding the accuracy of statistics gathered by the CDC. This correspondence will be referred to later in my answer.

The math of risk calculation (% risk associated with a procedure)

In order to do any comparison between statistics gathered on these procedures, one must first have an accurate numerator which is the number of times that an infection or a hemorrhage takes place in a chemical, surgical or spontaneous abortion, or a pregnancy.

Then, one must have an accurate denominator which is the total number of times that a chemical abortion has taken place, or the total number of surgical abortions, or the total number of spontaneous miscarriages or the total number of pregnancies ending in birth at term.

First consider the **Denominator in mifepristone abortions:**

If the denominator (the total number of procedures) is falsely high, then the risk attributed to the procedure will be falsely low, (just as 1/5 is less than 1/3) So, in the case of chemical abortion, it is very significant that Danco cannot give the exact number of chemical abortion procedures done.

Danco had been required to keep a count of all doses of mifepristone sold. However, those "doses" were packaged in a container of three 200mg pills, to give a total package dose of 600mg as approved by the FDA. Each package was to be accounted for by the manufacturer, and thus provide a baseline count of the number of procedures done.
But when Danco distributed these "packages" to abortion clinics knowingly violating the FDA regimen, it became impossible to trace the number of procedures done, because each packet could now represent 1 procedure, or as many as 3 procedures. So, when the investigation of the C. sordellii deaths began, Danco was contacted by the CDC to provide a number of procedures performed with mifepristone, in order to obtain an accurate denominator.

However, Danco was unable to provide an accurate denominator, but rather

guesstimated the number by taking the number of packets sold, assuming that 10% of the packets were stocked, then multiplying the remaining 90% by 3.
(See discussion of the calculation of the number of abortions done in the attached paper by Fischer of the CDC on the C. sordellii deaths). This number of 460,000 quoted in the Fischer article represents the maximum number of abortions that could possibly have been done, assuming that all of the abortions in the country were done using an off-label dosing of 200 mg of mifepristone. Thus, the denominator for all of the calculations of risk for mifepristone abortions is falsely elevated, and represents in reality the MINIMAL risk associated with mifepristone abortions. (The maximal risk is actually 3 times higher, if we assume that all abortions in the country were done using the FDA protocol) The real risk lies somewhere in between.

So, in the case of the risk of death from C. sordellii sepsis in mifepristone abortions, (assuming that we are able to know the real numerator, which I will get to in a moment) if we assume that 4 is the real numerator at the time of the Fischer CDC paper, then the minimum risk of death is 4/460,000 or a little more than 1/100,000 as reported in the paper. However, the maximum risk of death is 12/460,000. The real risk lies between these two numbers (assuming the numerator of 4 is correct)

Next, consider the **Numerator in mifepristone abortions.**

Calculations of risks of an event in mifepristone abortions depends on knowing how many events actually happened. To determine how many adverse events happen in a mifepristone abortion, Danco is relying on the number of adverse events reported through the voluntary AER reporting system.

However, FDA explicitly states that the AER reporting system cannot be relied upon to calculate risk ratios. FDA spokespeople have stated in previously published communications that the AER system only captures between 1 and 10% of the actual adverse events which occur. And while recent FDA spokespeople have stated that in the case of mifepristone they **believe** that all the adverse events are being reported for mifepristone, they have provided no objective evidence that it is true. One may as easily state that one does **not believe** that all the events are being reported, and in fact there is more objective evidence for this position.

This calculation of numerator is the reason why FDA put as a postmarketing restriction, the requirement of a postmarketing study to be done by Danco which looked prospectively at the real outcomes of abortions terminated with mifepristone. . Only a prospective study of the actual outcome of mifepristone abortions could reveal the true number of adverse events resulting from mifepristone abortions. This postmarketing study was never done.

There is good reason to believe that the number of AERs reported to Danco and the FDA is a gross underestimation of the actual number of adverse events. The AER system depends on a medical personnel who sees the patient to recognized that the adverse event is related to mifepristone use. However, the medical personnel who most often treats the mifepristone abortion patients who are hemorrhaging or infected is the ER doctor, who does not have access to the woman's abortion records. If the woman does not choose to tell the ER doc that she has had an abortion, then there would be no way for the ER doctor to know or recognize that this adverse event is related to an abortion. This is especially true for minors, who are often brought to the ER by parents, and for whom the minor may have great hesitancy in revealing that an abortion has been undertaken. Older patients also may be hesitant to reveal the history of mifepristone abortion which would now appear in their medical record. Thus it is very likely that the number of AERs reported for mifepristone represent a gross underestimation of the actual number of adverse events that mifepristone is responsible for.

Errors in calculation of live birth mortality

See letter from Weber to Tommy Thompson, and the reply to Weber from Gerberding, Director of CDC.

The essence of the exchange is as follows:

Normally to calculate the risk of death during some event, one would take the numerator to be the number of women who died during some event and put it over the denominator of the total number of women who had that event.

However, in calculating "maternal mortality" from carrying to term, the CDC takes the number of women who have died during pregnancy at **all gestational ages of all pregnancy related causes** and puts this number over the number of live births. Now the number of women who have died at all gestational ages includes women who have died from elective abortions, spontaneous abortions, ectopic pregnancies, cancers,and live births all together. See Pregnancy Related Mortality Surveillance U.S. 1991-1999 (MMWR Feb 21, 2003) attached.

Now, according to the MMWR Pregnancy Related Mortality Surveillance, under Figure 5, The distibution of pregnancy related deaths are attributed as follows:

60% of pregnancy related deaths are related to live births
10% of deaths are related to undelivered pregnancies (woman died while still pregnant at any gestational age)
7% of deaths are related to stillbirths (infant born dead)
6% of deaths are from ectopic pregnancies
0.3% of deaths are from molar pregnancies

Then note:
4% of deaths are directly attributable to abortions
13% are deaths attributed to "an unknown outcome of pregnancy".

All of these are summed up in the term "maternal deaths".

Now, as Gebherding has stated, the live birth component of this statistic is highly reliable. Virtually all live births are recorded. So to fall into a catagory of "unknown outcome of pregnancy" and have a death means that the possibility that this happened during a live birth is almost nil. The overwhelming likelihood is that deaths in this catagory, where the woman was known to be pregnant, then no one knows what happened to the fetus, are most likely to come from induced abortions.

As pointed out in the Weber letter, and as confirmed by Gerberding as well, is the fact that live birth mortality is calculated as the number of "maternal deaths" over the number of "live births". The MMWR also confirms this within the text of the report

"In this report, a woman's death was classified as pregnancy-related if it occured during pregnancy or within 1 year of pregnancy and resulted from 1) complications of pregnancy, 2) a chain of events that was initiated by the pregnancy, or 3) the aggravation fo an unrelated condidtion by the physiological effects of the pregnancy or its management." (MMWR Pregnancy Related Mortality Surveillance U.S. 1991-1999 (MMWR Feb 21, 2003)).

Now, this "maternal mortality" number is not the number of women who die from complications of live birth, which would in fact be actually 60% of the "maternal mortality" number, as per the distribution in Figure 5. However, this "maternal mortality" number is used by implication as the risk of carrying a pregnancy to term, as in the CDC article by Fisher on the C. sordellii deaths:

"There are no available incidence data for pregnancy-related C. sordellii infections or toxic shock syndrome. However, overall rates of infection-related deaths after pregnancy are well described. from 1991-1999, 259 maternal deaths due to infection were identified after 35,701,875 live births in the United States (footnote reference to the MMWR report Pregnancy Related Mortality Surveillance U.S. 1991-1999 MMWR Feb 21, 2003)."

Thus Fisher uses data that were generated by CDC using the definition of "maternal deaths" as defined within the document and quoted above to include deaths related to live birth, abortion, ectopics, stillbirths, molar pregnancies and pregnancies with *unknown outcomes*" Note also that the quote by Fisher above states "infection related deaths after *pregnancy*" (italics mine) not infection related deaths after live births.

Then note what that number is compared to a few paragraphs later:

"From 1988-1997 25 maternal deaths attributed to infection after surgical abortion were reported after 13, 161, 608 surgical abortions at any point in pregnancy"

Consideration of the article by Saul points out the inherent errors in this estimate, which come from lack of mandatory reporting of abortions themselves and the complications resulting from those abortions.

Thus, any comparison between the "risk of carrying a pregnancy to term" and the "risk of abortion" must keep in mind the sleight of hand being used in abortion statistics comparisons, and the abysmal lack of accuracy in the reporting of number of abortions and abortion related deaths and complications.

8. In your testimony you highlighted the risk of hemorrhage associate with this drug. What are the medical reasons that this drug predisposes women to hemorrhage?

It has been demonstrated from Spitz in the publication of the results of the U.S. clinical trial, that mifepristone abortions will fail 8% of the time when the woman is < or = to 49 days, and this failure rate will increase to almost one out of every 4 women (23%) who uses mifepristone at 57-63 days gestation. As stated in the Spitz article, "Failures, defined as cases requiring surgical intervention for medical reasons, or because the patient requested it, or the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of pregnancy." (Table one of the Spitz article shows that surgical intervention "because the patient requested it" accounts for 18/295 total failures or about 6%.)

When mifepristone abortions fail, there is most often placental tissue left inside. As long as the uterus has placental tissue, the blood supply from the mother will continue to be available to the placental bed. If this tissue begins to separate, then it will bleed, sometimes heavily. This is the mechanism of bleeding which occurs in both spontaneous abortions and in mifepristone abortions.

However, what separates bleeding in spontaneous abortions from bleeding in mifepristone abortions is the huge volume of blood lost in mifepristone abortions. The mechanism of this huge amount of bleeding in mifepristone abortions is not clear. What is clear from multiple articles is that the volume of bleeding noted with some studies of mifepristone abortions far exceeds the volume of bleeding in spontaneous abortions, as evidenced by the rate of necessity for emergency curettage and the rate of transfusions. See Harrison testimony submitted previously.

One theory is that the lower levels of pregnancy hormones circulating in a woman's body during spontaneous abortion result in smaller placental volumes and thus less surface area from which to bleed. In comparison, mifepristone abortions are done on viable fetuses which have normal levels of circulating pregnancy hormones, and normal placental volumes and thus more surface area from which to bleed.

It may also be possible that mifepristone or misoprostol may have a direct effect on blood vessel constriction of the spiral arteries which make up the maternal placental bed. There is some indirect literature to support this thought.

Respectfully submitted,

Donna J. Harrison, M.D.

Attachment 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
FOOD AND DRUG ADMINISTRATION
NATIONAL INSTITUTES OF HEALTH

Emerging Clostridial Disease Workshop
May 11, 2006
Atlanta, Georgia

Summary of Proceedings

Revised 6-22-06

TABLE OF CONTENTS

Page

Attachment 1: List of Participants
Attachment 2: Acronyms Used In This Report

Workshop Report 1
  Opening Session 1
  Panel 1-Session 1: Clinical Syndromes, Pathophysiology and Host Factors of *C. Difficile* 3
    Clinical Aspects of *C. Difficile*-Associated Disease 3
    Pathogenesis and Host Response of *C. Difficile* 5
    Regulation of *C. Difficile* Toxin Gene Expression 7
    Toxins of *C. Difficile* 8
    Panel 1-Session 1 Discussion 10
  Panel 1-Session 2: Clinical Syndromes, Pathophysiology and Host Factors of *C. Sordellii* 11
    C. Sordellii Toxic Shock Syndrome Following Medical Abortion 12
    An OB/GYN View of Early Medical Termination and *C. Sordellii* Infection 15
    Clinical Settings, Diagnostic Clues and Pathogenic Mechanisms of *C. Sordellii* 17
    The Pathophysiology of Mifepristone-Induced Septic Shock Due to *C. Sordellii* 19
    Bacterial Toxin Repression of Nuclear Hormone Receptors: Host-Pathogen Hormone Interactions and Implications for Therapy 21
    Panel 1-Session 2 Discussion 24
  Panel 2: Surveillance for Disease and Sources of Infection 25
    Federal and International Initiatives 25
    State Initiatives and Performance Characteristics of Optimal Surveillance Systems 28
    Panel 2 Discussion 30
  Panel 3: Identifying a Research Agenda 32
    Panel 3 Discussion 35
  Summary of Key Findings 37
  Closing Session 38

ATTACHMENT 1

List of Participants

Expert Panel Members

Dr. Jimmy Ballard
Oklahoma Health Sciences Center

Dr. John Bartlett
John Hopkins University School of Medicine

Dr. Gail Cassell
Eli Lilly and Company

Dr. Jeffrey Engel
North Carolina Department of Health

Dr. Marc Fischer
Centers for Disease Control and Prevention

Dr. Dale Gerding
Hines Veterans Affairs Hospital &
Loyola University Stritch Medical School

Dr. Ciaran Kelly
Harvard Medical School

Dr. Clifford McDonald
Centers for Disease Control and Prevention

Dr. James McGregor
University of Southern California
Keck School of Medicine

Dr. Ralph Miech
Brown Medical School

Dr. Abraham Sonenshein
Tufts University School of Medicine

Dr. David Soper
Medical University of South Carolina
Dr. Esther Sternberg
National Institute of Mental Health,
National Institutes of Health

Dr. Dennis Stevens
Veterans Affairs Medical Center

Congressional Staff, HHS Representatives and Members of the Public

Ms. Patricia Abruzzo
Dr. Michael Aldape
Dr. William Alexander
Ms. Amy Allina
Dr. Frederick Angulo
Dr. Laurie Archbald-Pannone
Ms. Sandra Arnold
Ms. Robyn Atkinson
Dr. Kevin Ault
Mr. Eugene Bachean
Ms. Traci Baird
Dr. Joseph Belanoff
Ms. Stacie Bell
Dr. Stephen Benoit
Ms. Cynthia Berg
Dr. Delia Bethell
Dr. Julu Bhatnagar
Dr. David Blaney
Mr. Dave Boyer
Dr. Colin Broom
Mr. Charlie Brown
Dr. Amy Bryant
Dr. William Callaghan
Dr. Denise Cardo
Dr. Roberta Carey
Mr. Robert Carman
Dr. Laura Castleman
Dr. Adam Cohen
Mr. Robert Colleluori
Ms. Jennifer Couzin
Mr. Mark Crawford
Dr. Dale Crockett
Dr. Susan Crockett

Dr. Vanessa Cullins
Dr. Scott Curry
Mr. Matthew Curtis
Dr. Carrie Cwiak
Dr. Andre Dascal
Dr. David Davidson
Dr. Daniel Davis
Mr. Christopher Delaney
Mr. Ken Dewar
Dr. Sandra Dial
Mr. Peter Donaldson
Ms. Dieu-Phuong Duranteau
Dr. John Dyke
Dr. Drick Dubberke
Dr. Ilana Dzuba
Dr. Paul Fine
Dr. Sydney Finegold
Dr. Lawrence Finer
Ms. Mary Fjerstad
Mr. Vince Forgetta
Dr. Victoria Fraser
Mr. Christopher Gacek
Dr. David Gardiner
Dr. Steven Gelone
Dr. Rachel Gorwitz
Ms. Michelle Gress
Mr. Jeffrey Hageman
Ms. Elaine Hamm
Dr. Shankar Hariharan
Ms. Kathleen Harriman
Mr. Gardiner Harris
Dr. Donna Harrison
Dr. Richard Hausknecht
Mr. Danylo Hawaleshka
Ms. Susan Heavey
Ms. Rebecca Hudson
Dr. Daniel Jernigan
Mr. Eric Johnson
Dr. Leslye Johnson
Dr. Robin Jump
Dr. Marion Kainer
Ms. Karen Kessnick
Dr. Rima Khabbaz
Ms. Erin Kiernon
Mr. George Killgore
Dr. Jeffrey Klinger
Mr. John Kools
Ms. Mary Kosinski
Dr. Melissa Kottke
Dr. Lynn Kramer
Ms. Beth Kruse
Ms. Preeta Krishnan Kutty
Dr. Sandra Kweder
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Dr. William Ledger
Ms. Coralee Lemley
Mr. Clement Lewin
Dr. Felicia Lewis
Mr. Jeffrey Lichtman
Ms. Brandi Limbago
Dr. Vivian Loo
Ms. Vernitta Love
Mr. David Lyerly
Ms. Jodi Magee
Mr. Bruce McClane
Ms. Betsey McKay
Dr. Robin McKenzie
Ms. Deirdre McQuade
Dr. Melody Mills
Ms. Roberta Mitchell
Dr. Scott Monroe
Ms. Kristen Moore
Dr. Jennifer Nelson
Dr. Lai-King Ng
Ms. Judith Noble-Wang
Dr. Randall O'Bannon
Mr. Barry Osborne
Ms. Jessica Parenti
Mr. Monty Patterson
Dr. Jacques Pepin
Dr. Samuel Posner
Ms. Kathleen Quinn
Ms. Judith Randal
Dr. David Rimland
Dr. Paul Riska
Dr. Roger Rochat
Dr. Gary Roselle
Ms. Nadine Rouphael
Ms. Anne Marie Ryberg
Dr. Robert Salata
Mr. Roger Sanderson
Dr. Clare Schmitt

Ms. Naoim Seller
Dr. Paul Seligman
Dr. Daniel Shames
Mr. Wun-Ju Shieh
Dr. Shy Shorer
Ms. Joanne Siberner
Dr. Didier Sicard
Dr. Marni Silverman
Dr. Mary Singer
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Mr. Glenn Songer
Dr. Arjun Srinivasan
Dr. Robert Steinbrook
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Dr. Cynthia Summers
Dr. Alexandra Tait
Dr. Hong Tang
Ms. Lynn Thogersen
Ms. Angela Thompson
Ms. Mischelle Thompson

Dr. Francesca Torriani
Mr. Hien Trinh
Ms. Miriam Tucker
Dr. Saul Tzipori
Dr. Kathleen Uhl
Dr. Francisco Uzal
Mr. Johannes vanDam
Dr. Lillian Van de Verg
Ms. Helena Von Hertzen
Dr. Jeffrey Waldman
Dr. Michel Warny
Mr. Kenneth Wilmarth
Dr. Beverly Winikoff
Dr. Christopher Woods
Ms. Wendy Wright
Ms. Suzanne Zane
Ms. Julie Zawisza

Mr. Erik Speakman, Facilitator

ATTACHMENT 2

Acronyms Used In This Report

B. subtilis — *Bacillus subtilis*
CA — Community-Associated
CDAD — *C. Difficile*-Associated Disease
CDC — Centers for Disease Control and Prevention
C. difficile — *Clostridium difficile*
CO — Community-Onset
C. sordellii — *Clostridium sordellii*
EIP — Emerging Infections Program
FDA — Food and Drug Administration
GI — Gastrointestinal
GM-CSF — Granulocyte Macrophage-Colony Stimulating Factor
HA — Healthcare-Associated
IDSOG — Infectious Disease Society of Obstetrics and Gynecology
LPS — Lipopolysaccharide
LTCF — Long-Term Care Facility
MIAs — Medically-Induced Abortions
MMWR — *Morbidity and Mortality Weekly Report*
NIH — National Institutes of Health
NNDS — Nationally Notifiable Disease System
OB/GYN — Obstetrical/Gynecological
PCR — Polymerase Chain Reaction
PPIs — Proton Pump Inhibitors
TSS — Toxic Shock Syndrome
VA — Veterans Affairs
WBC — White Blood Cell

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
FOOD AND DRUG ADMINISTRATION
NATIONAL INSTITUTES OF HEALTH

EMERGING CLOSTRIDIAL DISEASE WORKSHOP
May 11, 2006
Atlanta, Georgia

Workshop Report

The Department of Health and Human Services, Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and National Institutes of Health (NIH) convened the Emerging Clostridial Disease Workshop. The proceedings were held on May 11, 2006 at CDC's Global Communications Center in Atlanta, Georgia. The list of participants is appended to the report as Attachment 1.

The goal of the public workshop was to identify research needs and priorities to enable rapid progress in understanding the virulence, pathogenesis, host factors and non-antimicrobial risk factors contributing to reports of morbidity and mortality associated with *Clostridium difficile* (*C. difficile*) and *Clostridium sordellii* (*C. sordellii*). The workshop would also result in a draft research agenda with recommendations for detecting cases and conducting surveillance of diseases and organisms.

Opening Session

Dr. Rima Khabbaz is the Director of the CDC National Center for Infectious Diseases. She welcomed the participants to the workshop and emphasized that CDC hopes the workshop will assist in focusing research and prevention efforts related to *C. difficile* and *C. sordellii*. CDC is committed to strengthening its knowledge on the tremendous morbidity, significant mortality and increased disease severity associated with these serious and challenging infections. Dr. Khabbaz confirmed that CDC will respond to the input, recommendations and next steps provided during the workshop on research and surveillance to address *C. difficile* and *C. sordellii*.

Dr. Paul Seligman is the Associate Director for Safety, Policy and Communication in the FDA Center for Drug Evaluation and Research. He also welcomed the participants to the workshop and explained that reports have been emerging in the United States over the past few years on serious *C. difficile* and *C. sordellii* infections. *C. difficile* is a toxin-produced anaerobe that primarily occurs with antibiotic use and is generally manageable with established therapy. *C. sordellii* was believed to rarely produce toxins or clinical illness.

In 2005, however, CDC published reports of unusual patterns and characteristics of *C. difficile* and also published a case series of deaths from *C. sordellii*. These clusters raised important public health questions about *Clostridium*'s microbiologic ecology and its relationship to fatal illnesses and pregnancy. CDC, FDA and NIH acknowledge the critical need to vigorously approach these issues with scientific rigor, conduct research, and perform surveillance to mitigate public health effects of *C. difficile* and *C. sordellii*.

Dr. Seligman described individual and collective actions CDC, FDA and NIH will take to fill data gaps in *C. difficile* and *C. sordellii*. Jointly, the agencies will thoroughly review and discuss input and recommendations provided during the workshop as well as additional information submitted to the public docket. Each agency will post the workshop transcript, summary and materials submitted to the docket on its respective web site for public access and review. The agencies will produce a draft research agenda with recommendations for detecting cases, conducting surveillance, and enhancing knowledge of the virulence, pathogenesis and treatments for *C. difficile* and *C. sordellii*. The agencies will publish proceedings of the workshop in a peer-reviewed medical journal.

Individually, CDC will closely analyze additional types of monitoring for healthcare-associated (HA) *C. difficile* infections and emerging community-associated (CA) infections. New and evolving risk factors for these diseases will be defined. Definitions and strategies will be developed to better monitor *C. sordellii* infections.

FDA will establish realistic time-lines for obtaining more knowledge on the pathophysiology and etiology of *C. difficile* and *C. sordellii* and determining whether regulatory action affecting the appropriate use and availability of these drug products is warranted. NIH will continue to lead research on the pathogenesis and biology of emerging infections. Efforts will be made to encourage the research and product development communities to address *C. difficile* and *C. sordellii* in future research proposals.

PANEL 1-SESSION 1: CLINICAL SYNDROMES, PATHOPHYSIOLOGY AND HOST FACTORS OF *C. DIFFICILE*

The Panel 1-Session 1 speakers made presentations to define the current emerging clinical syndrome, knowledge gaps and recommendations for basic, applied and clinical research for *C. difficile*. The four Panel 1-Session 1 presentations are outlined below.

Clinical Aspects of *C. Difficile*-Associated Disease (CDAD)

Dr. Dale Gerding is the Associate Chief of Staff for Research and Development at the Hines Veterans Affairs (VA) Hospital. He covered the following areas in his presentation. CDAD is acquired by ingestion of *C. difficile* spores. Prior antibiotic exposure places patients at risk for CDAD. Diarrhea that is mediated by toxins is the most common symptom of *C. difficile*, but severe colitis, sepsis and death may also result. FDA has not approved the use of metronidazole, rifaximin or nitazoxanide for treatment of CDAD.

The current hypothesis is that CDAD occurs usually among hospitalized patients who have taken antibiotics and acquired a toxigenic strain of *C. difficile* but fail to mount an anamnestic IgG antibody response to toxin A. The four major clinical problems with the disease are (1) an inability to prevent CDAD in hospitals and other high-risk settings; (2) the lack of a sensitive and rapid diagnostic test for CDAD; (3) the absence of a treatment to prevent recurrence of CDAD; and (4) an inability to effectively treat fulminant CDAD.

Several general principles are applied to diagnose CDAD. Stool culture is the most sensitive test for CDAD; the cell cytotoxin assay is the most specific test; and the enzyme immunoassay for toxins A and B is the most widely used test to diagnose CDAD based on a survey that was recently administered to infection control and disease physicians, but is only about 70% as sensitive as culture. Flexible sigmoidoscopy is rapid, but only has a 50% sensitivity rate in detecting pseudomembranes. A rapidly rising white blood cell (WBC) count is a clue to fulminant CDAD.

In terms of current options for the treatment of CDAD, metronidazole and vancomycin are antimicrobial drugs that disrupt the flora and leave ~20% of patients susceptible to recurrence, relapse with the same organism or re-infection with a new organism. Newer treatment possibilities include very narrow spectrum antimicrobial drugs, toxin-binding agents, biological agents that prevent re-colonization, and active and passive vaccines.

A paper published in 2006 on the treatment of the first recurrence of CDAD showed the CDAD recurrence rate was correlated with age and length of hospital stay. Metronidazole was not found to be inferior to vancomycin for treatment of the first recurrence of CDAD. Treatment of the first recurrence of CDAD with the same or a different agent made no difference in outcomes. Complications of shock, colectomy, perforation, megacolon or death were seen in 11% of patients with the first recurrence. This rate was higher than previously observed and is a caution to institute treatment of recurrences rapidly.

A paper published in 2002 on multiple recurrences of CDAD showed the risk of a subsequent CDAD episode in patients with a previous recurrence was 45%. New *C. difficile* organisms caused 50% of recurrences. Anecdotal support was demonstrated for many empiric treatments, such as vancomycin regimens, biotherapeutic approaches, passive treatment with immunoglobulin, toxin-binding agents, and fecal reconstitution using espousal donors, however, no adequate randomized controlled trials are available.

New clinical issues are emerging for *C. difficile*. CDAD rates are increasing and a common epidemic strain was detected in the United States, Canada and Europe. More severe CDAD is being observed with higher rates of mortality and colectomy. The efficacy of metronidazole treatment is now being questioned. Disease in the community and peripartum cases may be increasing. The use of proton pump inhibitors (PPIs) may increase the risk for CDAD. Discharge data show that CDAD rates doubled in VA hospitals from 2000-2004 and similar rate increases are occurring in all US hospitals.

A additional toxin known as binary toxin, variations in the *tcdC* gene and high-level resistance to fluoroquinolone antibiotics have been identified as three characteristic virulence factors of new strains. Fulminant CDAD appears to be increasing. Patients with fulminant disease may exhibit toxic megacolon, hypotension, sepsis, ileus or perforation. A rapid rise in WBC counts may be a clinical clue. Delivery of antibiotics to the site of infection may be difficult. Surgical removal of the colon may be life-saving. Controlled trials to better manage patients and an improved clinical algorithm to decide on surgery are critical needs at this time.

Three recent publications have raised controversies about the continued efficacy of metronidazole in treating CDAD. All three papers showed a higher failure rate of the drug in treating CDAD. Response rates decreased from ~95% to ~75%, while recurrence rates increased from ~20% to ~30%. CDC received voluntary reports from four states over a 28-month period of 23 CA-CDAD cases and 10 peripartum CDAD cases. Of the CA-CDAD cases, 24% reported no antibiotic use in the previous three months. Of the two isolates recovered, both had the binary toxin gene, one had the *tcdC* gene deletion, and neither was the new epidemic strain. Of four particularly severe peripartum CDAD cases among pregnant women 20-31 years of age, three died and one underwent colectomy.

Data from a U.K. general practice database were published in 2005 and showed alarming increasing rates of CA-CDAD. The rate of CA-CDAD increased from 1/100,000 to 22/100,000 in a ten-year period. The data showed a significant but far lower rate of antibiotic exposure than expected, significant rates of exposure to PPIs other antacid drugs and significant exposure to non-steroidal anti-inflammatory drugs. All of these new and emerging clinical issues emphasize the critical need for stronger research and strategies to prevent and treat CDAD.

Pathogenesis and Host Response of *C. Difficile*

Dr. Ciaran Kelly is the Associate Professor of Medicine at Harvard Medical School. He covered the following areas in his presentation. Colonic luminal concentrations and colonization resistance influence antibiotic susceptibility of *C. difficile* isolates. Antibiotic therapy disrupts colonization resistance of colonic microflora, but this area warrants further study. Research is also needed to identify antibiotics that are effective in treating *C. difficile*, but do not cause critical changes to the colonic microflora.

Ampicillin, amoxicillin, cephalosporins, clindamycin and quinolones are the antimicrobial agents that most frequently induce CDAD and colitis. However, patients may develop CDAD through cytotoxic chemotherapy, colon preparation or inflammatory bowel disease without antibiotic use. Non-antibiotic-associated CDAD is rare in hospital settings, but may be more common in the community. Two published studies showed that only 36% and 65%, respectively, of CA *C. difficile* patients had a documented history of antibiotic use.

Exposure to *C. difficile* is more likely to occur in healthcare institutions. A high number of spores are present in these facilities and both the environment and personnel can act as sources of *C. difficile*. A published study demonstrated the ability to culture *C. difficile* from several hospital locations and staff. Another study was conducted on the prevalence and acquisition of *C. difficile* among ~300 patients on antibiotics in a high-risk medical ward with a stay of >2 days. The study showed that 31% of the cohort was colonized at some point during the hospital stay. However, ~50% of colonized patients will not develop disease, while the remaining 50% will develop CDAD.

Toxin A was historically believed to be more important than toxin B due to its enterotoxic effect in animals. However, recent human studies and clinical observations have called this traditional theory into question. Data show that toxin B has an equal or greater injurious effect to the colon than toxin A in colonic explants and intestinal xenographs. Moreover, a small number of toxin A-negative/toxin B-positive strains of *C. difficile* were found to cause significant disease in humans, including severe pseudomembranous colitis. Both toxins A and B cause diarrhea and colitis. These data suggest that both toxins A and B are important in causing disease and need to be addressed by new agents.

In addition to antibiotic use, age, co-morbidity, and innate and adaptive immune responses also serve as host factors to CDAD. Further research on the role of corticosteroids and the innate immune response in fulminant CDAD should be explored. The relationship between the adaptive immune response and CDAD also warrants further study because ~60% of humans have serum IgG and colonic IgA antitoxin antibody. The current hypothesis is that the host immune response plays a pivotal role in determining the clinical outcome of infection with toxigenic *C. difficile*.

A study published in 2000 demonstrated high serum IgG antitoxin A levels in asymptomatic carriers of *C. difficile*. Another study published in 2001 showed high serum IgG antitoxin A levels were associated with a lower risk for recurrent CDAD. These data suggest that a primary immune response during a *C. difficile* episode appeared to be associated with protection against recurrence.

Recent data and increased knowledge of the pathogenesis of CDAD provide opportunities to intervene at different points in the progression of disease. The control of antibiotic therapy and prevention of exposure on colonization will continue to serve as important interventions. A memory response accounts for asymptomatic carriers and a primary immune response assists in protecting against recurrence. Newer antibiotics that are now being studied show promise in terms of having a narrower spectrum of activity and a smaller potential to be associated with recurrence.

The targeted probiotic approach of using a non-toxigenic strain of *C. difficile* to purposely infect the patient and prevent infection with a toxigenic strain is worthy of additional study. Data from the current Phase III tolevamer trial demonstrate promise as a non-antibiotic strategy for treatment of *C. difficile*. A toxoid-based vaccine is currently in Phase II studies. Several approaches for passive immunotherapy are being considered as mechanisms to protect high-risk persons, such as intravenous immunoglobulins, monoclonal antibodies against toxins A and B, and production of a hyper-immune globulin from vaccinated individuals who undergo plasmapheresis.

Regulation of *C. Difficile* Toxin Gene Expression

Dr. Abraham Sonenshein, of the Tufts University School of Medicine, covered the following areas in his presentation. The relationship between *C. difficile* sporulation and pathogenesis produces three major outcomes. Spores act as a reservoir of disease-causing organisms. Germination in the gastrointestinal (GI) tract is essential for pathogenesis. Toxins A and B are only synthesized during sporulation or the stationary phase. *C. difficile* would be unable to produce toxin, sporulate in the gut or spread disease if the organism had no ability to germinate in the gut. Cells can only sporulate in response to a nutritional limitation.

The onset of sporulation is accompanied by other adaptive responses, such as motility and chemotaxis, secretion of degradative enzymes, transport of secondary nutrients, intracellular catabolic pathways, genetic competence, and antibiotic and toxin production. Spo0A~P is a major transcription factor for early sporulation genes, while RNA polymerase sigma factors, dissociable subunits that direct RNA polymerase to specific promoter sites, turn on large groups of genes at specific times and in specific compartments of the spoulating cell. All sporulation-specific sigma factors are recognizable in *C. difficile*. *TcdR* is a sigma factor for toxin gene transcription that is used for stressful conditions and the control of toxin synthesis.

The C. difficile pathogenicity locus includes five genes. In addition to *tcdB* and *tcdA* genes, which encode two toxin proteins, the *tcdE* gene is suspected of encoding a holing- like protein. This protein may be responsible for the release of toxins into the environment. The *tcdR* upstream gene is believed to act as regulatory protein. Recent studies demonstrate that *tcdR* protein is one of the alternative sigma factors for RNA polymerase. The protein interacts with the RNA polymerase core to direct the enzyme to specific promoter sites for tcdA, tcdB and the *tcdR* gene.

The *tcdR* gene controls toxin synthesis in *C. difficile* and is also closely related to genes that control toxin synthesis or bacteriocin production in *C. botulinum*, *C. tetani* and *C. perfringens*. A previous study demonstrated that the timing of toxin synthesis at protein and messenger RNA levels occurred at the end of rapid exponential growth. Spore formation is not believed to be essential for toxin synthesis, but a clear regulatory connection exists between these two processes. No expression of toxin genes was found at any time during the growth cycle in the presence of glucose in the medium.

Three physiological issues must be addressed to better understand the regulation of *C. difficile* toxin gene expression: (1) the metabolic signal for nutrient deprivation; (2) the regulatory protein that senses the metabolic signal; and (3) the controlling mechanism between regulatory protein and expression of toxin genes. Previous studies on *Bacillus subtilis* (*B. subtilis*) were used as a model to try to understand this regulation.

The B. subtilis CodY protein serves as a repressor of hundreds of genes that are normally turned on as cells experience nutrient limitation. CodY homologs are nearly ubiquitous in low G+C gram-positive bacteria. CodY recognizes the GTP nucleotide and isoleucine amino acid or valine simultaneously in the cell. *B. subtilis* was used as a surrogate organism due to the inability to produce a CodY mutation in *C. difficile*. The study was designed to determine whether inactivation of a codY gene in *B. subtilis* would affect the expression of *C. difficile* toxin genes.

The deletion of the codY gene in *B. subtilis* resulted in greatly enhanced synthesis of expression of a toxin gene. This finding suggested that the *Clostridium* system was under the control of CodY for *B. subtilis*, but the experiment has not yet been replicated in *C. difficile*. An in vitro experiment demonstrated that the CodY protein of *C. difficile* depends on both GTP and branched chain amino acids to tightly bind to DNA. The tightest site of binding was found to be between two putative promoters that drive expression of the tcdR gene.

The precise molecular mechanism is still unknown, but a model can be constructed for the expression of the *tcdR* gene. A related study showed that the tcdC gene encodes an anti-sigma factor blocking transcription of the A and B genes. A more refined model postulates that CodY protein acts as a negative regulator of the tcdR gene during rapid exponential growth and simultaneously stimulates transcription of the tcdC gene. When cells are in the stationary phase, CodY loses its ability to bind to DNA and stimulate tcdC gene expression. In the absence of a genetic system in *C. difficile*, however, this model cannot yet be confirmed.

Toxins of C. Difficile

Dr. Jimmy Ballard is an Associate Professor in the Department of Microbiology and Immunology at the Oklahoma Health Sciences Center. He covered the following areas in his presentation. From 1938 to the present, tremendous advancements have been made in the study of C. *difficile* toxins, including the initial discovery and analysis, preliminary understanding of cellular activities, additional knowledge in the enzymatic mechanism of action, and the current focus on the atomic level.

Toxins A and B are large clostridial and intracellular bacterial toxins in the type A subfamily of glucosyltransferases. The toxins are found in nearly all clinically-relevant isolates. Immunity to the toxins provides protection from CDAD. The toxins can disrupt cellular physiology; hydrolyze UDP-glucose; terminate signaling through proteins; and change cellular morphology, modulation of the mitochondria and important transcriptional impacts.

Rho, Rac and Cdc42 are small GTP-binding proteins that regulate various events and act as targets to toxins A and B. Studies have shown that other targets may also be important for intoxication, but additional research needs to be conducted in this area. Toxin A results in several effects at the *in vitro* or cellular level, including cell rounding, caspase activation, modulation of the mitochondria, mitogen-activated protein kinase activation, apoptosis and cell death, and increased permeability of epithelial barriers. At the *in vivo* or host level, the effects of toxin A are lethal with fluid accumulation in rabbit ileal loops, neutrophil recruitment, mast cells and macrophages, reactivation of oxygen intermediates, chemokines, cytokine production and neuronal impacts.

At the cellular level, toxin B intoxicates a wide variety of cell types and causes cell rounding, modulation of intracellular signaling pathways, caspase activation, disruption of tight junctions and numerous other impacts related to Rho proteins. At the host level, toxin B is lethal and may also cause systemic and enterotoxic effects. Many of the observed effects of toxin B may be directly attributed to the enzymatic domain.

Studies are underway focusing on the receptor binding domains of toxins A and B. The receptor binding domain can provide protection against the toxin in animal models and may have the ability to engage multiple receptors when interacting with target cells. However, additional research is needed because at least 24 different toxinotypes of *C. difficile* have been identified.

In addition to toxins A and B, *C. difficile* also produces a binary toxin with an A polypeptide that is enzymatic, functions as an ADP-ribosyltransferase and modifies actin in the cell. The binary toxin can be found in 6%-12% of isolates and is associated with recent epidemic strains of *C. difficile*. The binary toxin may also play an important role in colonization, but this area is poorly understood at this time.

The five members of large clostridial toxins are in the *C. difficile*, *C. novyi* and *C. sordellii* species with various levels of lethality. Studies were previously conducted to determine the frequency by which *C. sordellii* produces lethal toxin. An analysis of isolates from cadaver-derived tissue showed that only one produced *tcsL*, all produced a neuraminidase, and a few produced a phospholipase. The isolates also produced a cholesterol-dependent cytolsyin that is found in many *Clostridia* species.

CDC provided 25 clinical isolates of *C. sordellii* for the study, but not all of the isolates produced lethal toxin and many did not produce any detectable cytotoxic factor. Additional research is warranted in this area because these findings are inconsistent with the standard paradigm for *Clostridia*. Most notably, *Clostridia* are known to produce very strong and potent toxins that rapidly cause serious disease.

Several issues will need to be addressed in future studies to strengthen knowledge about *C. difficile* toxins, including (1) toxin B's specific *in vivo* effects and contribution to CDAD; (2) the impact of increased expression of toxins A and B during disease; (3) the overall profile of substrate targets in mammalian cells; (4) specific receptors for toxins A and B; (5) the role of the binary toxin in disease; (6) the contribution of *tcsL* and other toxins to disease; and (7) the mechanism of pathogenesis in isolates that do not appear to produce enterotoxins.

Panel 1-Session 1 Discussion

The Panel 1-Session 1 presenters provided additional details about the clinical syndromes, pathophysiology and host factors of *C. difficile* in response to questions and comments from the participants.

- The lack of selectable markers, methods for simple transformation and recombination are some of the issues that increase the difficulty in advancing genetic manipulation techniques for *C. difficile* and *C. sordellii*. Research is needed to produce a viable genetic system and answer fundamental questions about *C. difficile*. Technologies that might be applied include broad-host-range plasmids, gram-positive conjugated transposon Tn916, suicide plasmids and antisense RNA. However, more progress in genetics is expected to be made with *C. sordellii* because this organism is more sensitive than *C. difficile* to a variety of selectable markers.
- The antibody response against *C. difficile* is typically acquired by 2-3 years of age. Neonates have an extremely high colonization rate and a

very low disease rate. Carriage of *C. difficile* in the GI tract is common in infants, but much lower in adults. Some research suggests that neonates and young infants do not express toxin receptors. Specific elements that make older persons more susceptible to *C. difficile* have not been identified at this time.

- Persons typically do not have high levels of colonization with *C. difficile* upon hospital admission, but patients generally acquire the organism at a rate of ~8% the longer the hospital stay. Data suggest that colonized persons who do not become ill are in a protected state.
- Minimal studies in humans have been conducted on colonization with *C. sordellii*. The published literature contains a paucity of stool or vaginal flora surveys for *C. sordellii*.
- Adherence factors of *C. difficile* are important, but have not been extensively studied. However, some research has shown that altering the microflora of the gut changes the levels and types of expression of glycans on the surface of the epithelium. This process could change binding sites and cause antibiotics to facilitate *C. difficile* colonization. Another study has described a putative adhesion factor in *C. difficile* surface layer proteins that may act as adhesives. Other data indicate that antibody against surface layer protein A has a statistically significant protective effect.
- The association between age and fasting achlorhydria should be analyzed in the context of gastrin levels or pepsinogen in serum. Additional research should also be performed on the role of the Charleson Index and other measures of global co-morbidity in *C. difficile*.
- Previous studies demonstrated that environmental contamination and carriers play an important role in spreading CDAD in hospitals. The data showed that 50% of sites in rooms of patients with diarrhea are contaminated with spores. Spores that are not physically removed or killed with bleach or hydrogen peroxide solutions can remain in the environment for several months. An overwhelming speculation is that contaminated hands of healthcare workers lead to the spread of spores to susceptible patients.
- Environmental sources of antimicrobial agents may perturb host-microbe relationships and disturb niches in the gut. Certain diets or food additives may predispose persons to *C. difficile*.

PANEL 1-SESSION 2: CLINICAL SYNDROMES, PATHOPHYSIOLOGY AND HOST FACTORS OF *C. SORDELLII*

The Panel 1-Session 2 speakers made presentations to define the current emerging clinical syndrome, knowledge gaps and recommendations for basic, applied and clinical research for *C. sordellii*. The five Panel 1-Session 2 presentations are outlined below.

C. Sordellii Toxic Shock (TSS) Syndrome Following Medical Abortion

Dr. Marc Fischer, of the CDC National Center for Zoonotic, Vector-Borne and Enteric Diseases, covered the following areas in his presentation. *C. sordellii* is a gram-positive anaerobic *Bacillus* that typically resides in soil and colonizes the GI and genital tracts of healthy humans. *C. sordellii* is not commonly found in surveys of stool and vaginal flora, but the organism was isolated from musculoskeletal tissues of 3% of cadaver donors in a recent study. Lethal and hemorrhagic toxins determine the virulence and clinical manifestations of *C. sordellii*. However, lethal toxin is variably expressed by different *C. sordellii* strains and its cytopathic effects are altered by environmental conditions.

Case reports have described *C. sordellii* as a cause of pneumonia, endocarditis, arthritis, peritonitis, corneal ulcer, bacteremia and wound infections, including necrotizing fasciitis, myonecrosis, tissue allograft infections, neonatal omphalitis, postpartum endometritis and episiotomy infection. Fulminant TSS among previously healthy persons has been reported in only a small proportion of *C. sordellii* infections. *C. sordellii* TSS is an acute and rapidly progressive disease that is characterized by a lack of or minimal fever; refractory tachycardia and hypotension with no response to intravenous fluids; local edema at the infected site with subsequent pleural and peritoneal fusions; a marked leukemoid reaction; and an elevated hematocrit due to hemoconcentration. *C. sordellii* TSS is fulminant and most often fatal.

From 1976-1993, six cases of *C. sordellii* toxic neonatal omphalitis were reported in the literature among infants 2-11 days of age. These cases were characterized by severe abdominal wall swelling, periumbilical erythema and discharge, and markedly elevated WBC counts. *C. sordellii* was isolated from the umbilicus, peritoneal fluid and blood. Five of these six patients died. From 1992-2000, four clusters of *C. sordellii* wound infections were reported among black tar heroin injecting drug users. Many of the infections contained *C. perfringens* and other soil contaminants. The presence of *C. sordellii* appeared to be associated with a toxic shock-like syndrome and a high case fatality rate.

In 2001, fatal C. *sordellii* sepsis and TSS were reported in a previously healthy male 23 years of age who received a contaminated tissue allograft. The case prompted a broader investigation that identified 13 additional cases of *C. septicum* or *C. bifermentans* infections associated with tissue allografts. None of the 13 cases were fatal. From 1977-2001, ten cases were reported in the literature of female genital tract infection and fatal TSS associated with *C. sordellii* among previously healthy women 23-40 years of age. Of the ten cases, all were fatal, eight occurred after delivery of live-born new infants, one occurred after a medical abortion, and one was not associated with pregnancy. Leukemoid reaction and hemoconcentration were the hallmark findings of these cases.

In 2000, FDA approved mifepristone plus misoprostol for medical termination of pregnancy up to seven weeks gestation. Mifepristone is a synthetic steroid with anti-progesterone and anti-glucocorticoid effects, while misoprostol is a prostaglandin analog that causes uterine contractions. The FDA-approved regimen is 600 mg of oral mifepristone followed within two days by 400 µg of oral misoprostol. From September 2003-June 2005, FDA received reports of four deaths among women who had recently undergone medically-induced abortions (MIAs) with mifepristone and misoprostol. The four patients received a common off-label regimen of 200 mg of oral mifepristone followed by 800 µg of vaginal misoprostol.

The initial investigation found that each case was consistent with fulminant toxic shock-like syndrome. In March 2004, FDA contacted the CDC Unexplained Deaths Project to assist in identifying a specific infectious etiology of the cases. The four women were white, black and Asian; 18-34 years of age and previously healthy; and residents of and obtained MIAs in California. The median time from receipt of mifepristone to onset of initial symptoms was five days. The time from hospitalization to death was <24 hours.

Of the four cases, one had a documented fever; none had a rash; all reported tachycardia, hypotension, vomiting or diarrhea, and severe abdominal pain; three had a significant leukemoid reaction; two had significant hemoconcentration; two had moderate thrombocytopenia; one had renal insufficiency; and none had elevated hepatic enzymes or bilirubin. Blood cultures performed on three patients prior to antibiotics were negative for bacteria. One vaginal swab obtained pre-mortem grew *Gardnerella* species. An endometrial tissue collected postmortem from one patient grew *Escherichia coli* and an anaerobic gram-positive *Bacillus*.

CDC's analysis of fixed tissues from autopsies showed pleural or peritoneal effusions and diffuse pulmonary edema in three of the four cases. None of the patients retained fetal or placental tissue. Hematoxylin and eosin stains of uterine tissue showed extensive acute inflammation and necrosis of the endometrium and myometrium in all four patients. Three patients had areas of edema and hemorrhage within the uterus. Two patients had multiple abscess formation.

Immunohistochemistry results on uterine tissue were positive in all four patients for *Clostridium* species; positive in one patient for *Staphylococcus aureus*; and negative in all four patients for both group A streptococcus and *Neisseria* species. Mixed bacteria were seen on gram stains of uterine tissue for all four patients, but abundant gram-positive bacilli were the predominant findings in each case. Histopathologic findings for all tissues other than the uterus were unremarkable. Extensive bacilli and granular antigens were seen in the areas of inflammation in the endometrium and myometrium.

Polymerase chain reaction (PCR) results were positive in all four patients for the broad-range 16S rRNA, *C. sordellii* 16S rRNA, *C. sordellii* cytotoxin L, and *C. sordellii* phospholipase C genes. The PCR results on uterine tissue were negative for the *C. perfringens* alpha toxin gene in all four patients. Based on the findings of the investigation, CDC concluded that the four deaths were attributed to *C. sordellii* endometritis and TSS. The clinical and pathologic findings were similar to ten other cases of *C. sordellii* genital tract infections previously reported in the literature. The cases demonstrated that serious infection can occur after MIAs.

Several issues are still unresolved regarding the possible association between the use of mifepristone and misoprostol and the risk of *C. sordellii* TSS, including changes in vaginal flora or environment, incomplete abortion with necrotic decidual tissue, immunosuppressive effects of mifepristone, increased pathogen virulence, altered host susceptibility, and the interaction of multiple factors. Product contamination was eliminated as a cause because no epidemiologic links were identified among the patients. Medications in the four cases were obtained from different clinics, healthcare providers and manufacturing lots. FDA tested both mifepristone and misoprostol from manufacturing lots received by the patients and found no contamination with *C. sordellii*.

A reporting or case detection bias was also considered as potential cause. Local and regional attention in California may have increased awareness among healthcare providers and the public and stimulated reports of additional cases that may have not been detected in other states. No centralized reporting system has been developed for pregnancy-associated infections or deaths. Laboratory confirmation of *C. sordellii* in the four cases resulted from extraordinary efforts by a national reference laboratory. FDA's MedWatch system initially detected the four cases and is designed to identify adverse events associated with approved medications.

In an effort to address these issues, CDC and its partners initiated several supplemental surveillance activities to identify additional cases of severe infection or TSS associated with pregnancy, childbirth or abortion. Articles were published in the *Morbidity and Mortality Weekly Report* (*MMWR*) and *New England Journal of Medicine* requesting that healthcare providers report any TSS cases associated with pregnancy or abortion to local health departments. Specific queries were sent to members of the Infectious Disease Society of Obstetrics and Gynecology (IDSOG), the National Association of Medical Examiners, and CDC's Unexplained Deaths Project sites. The California Department of Health Services initiated a retrospective review of death certificates to identify additional cases.

CDC hopes the workshop will be used as an opportunity to develop a research agenda and answer three key questions. One, are women who use mifepristone or misoprostol at increased risk of *C. sordellii* infection or TSS compared to other women following surgical abortion, spontaneous abortion or childbirth? Two, what is the mechanism of the increased risk? Three, is the risk limited to *C. sordellii* compared to other *Clostridium* or anaerobic bacteria? Four, what approaches can be taken to further reduce the risk and improve treatment of *C. sordellii* infections?

An OB/GYN View of Early Medical Termination and *C. Sordellii* Infection

Dr. James McGregor is a Visiting Professor of Obstetrics and Gynecology at the Keck School of Medicine. He covered the following areas in his presentation. Seven deaths from 560,000 early medical terminations that have been reported since 2000 demonstrate that this risk is higher than surgical termination. The traditional microbiologic paradigm may now be inadequate because the role of innate and acquired immunity and medications should also be considered. Three cases of *Clostridia* were unclassified in a 2005 published study that used basic nucleic acid techniques to identify the microbiology in the vagina among 78 patients.

In animals, *C. sordellii* is associated with malignant edema, bloat, hemorrhage and sudden death in sheep. In humans, *C. sordellii* causes pregnancy-associated infections, wound infections, edema and lethal toxic shock-like syndrome. *TcsL* is a large clostridial toxin that affects glycosylates; the Ras, Rac and Ral genes; and signaling within endothelial and myocardial cells. Previous research showed that increased acid pH disassociated and increased the potency of toxins. Intoxification increased five-fold and the intoxicating dose was lowered by one log at the optimal pH range of effect of 4.0-5.0. These findings suggest that local conditions in the uterus are important factors to consider in identifying *Clostridia* production.

Mifepristone was developed in 1981 and has generated >700 publications. The drug uses progesterone-dependent processes and is applied in the termination of early pregnancy, inhibition of follicular development, cervical ripening, glucocorticoid-dependent processes, breast cancer treatment, labor induction and endometriosis. However, mifepristone's unusually long half-life of 30 hours poses problems in titrating doses within a therapeutic range. Previous research on the pharmacokinetics of mifepristone among five females showed that the drug actively binds to the progesterone receptor in the endothelium and the affinity for glucocorticoid receptors. The affinity of mifepristone was found to be four-fold of dexamethasone.

Another study demonstrated that the effects of mifepristone persisted for one week and was excreted by methylation and hydroxylation. Metabolites are active in terms of both the progesterone and glucocorticoid receptors. A seminal study that was published in 1986 recommended close medical supervision in using mifepristone due to the potential for prolonged and abnormal bleeding. A study published in 2002 found mifepristone and misoprostol to be superior. The study further concluded that mifepristone alone may be acceptable when misoprostol is unavailable.

A retrospective study that was published in 2004 determined that medical early pregnancy termination can be accomplished without mifepristone. Misoprostol was found to be a satisfactory agent for medical abortion at a rate of 88%-96% in this setting. The drug was also administered to 34 patients during the study. Numerous studies on the innate immune response have demonstrated increased lethality in animal models with mifepristone. The drug enhanced *C. difficile* toxin A intestinal secretion and inflammation in a well-controlled clinical trial.

A letter was published in the *Annals of Pharmacotherapy* in 2005 to point out that vaginal application of misoprostol is prohibited in France where misoprostol can only be prescribed in oral form. However, other data from the Netherlands are well reported and serve as an excellent source of solid epidemiological information. A suggestion has been made for physicians in North America to more freely administer antibiotics at the initiation of a medical termination and give steroids if a patient becomes ill. However, other primary prevention strategies should be considered as well.

Consideration should be given to reducing or entirely eliminating mifepristone. The drug should only be administered orally as approved by FDA. Short- or long-course antimicrobial prophylaxis is not likely to be effective. Probiotics will most likely have minimal efficacy from a physiological perspective. Informed consent forms for misoprostol should be changed to more clearly acknowledge potential risks for serious infection or complications. Treatment and recognition of C. *sordellii*-associated TSS should be improved with a case definition and clearly described laboratory factors.

Patients with C. *sordellii*-associated TSS should be rapidly admitted to a healthcare facility, given consultations with infectious disease physicians and intensivists, and promptly provided with multiple organ support. A hysterectomy or dilation and curettage should be immediately considered for patients with a clear diagnosis of C. *sordellii*-associated TSS. Clindamycin, imipenen, IV/Ig protein C aspects and steroid support should be considered as well.

Modern technologies should be applied to study the sub-cellular, cellular organ and organismal effects of mifepristone and misoprostol and increase knowledge about the active epidemiology of C. *sordellii* in pregnant women and other populations. Existing models of mifepristone should be analyzed to conduct additional research on the pathophysiology of infection and inflammation. Studies should also be conducted on mifepristone and misoprostol metabolism. Active surveillance should be performed on the adverse effects of these drugs.

Clinical Settings, Diagnostic Clues and Pathogenic Mechanisms of *C. Sordellii*

Dr. Dennis Stevens, of the Boise, Idaho VA Medical Center and the University of Washington School of Medicine, covered the following areas in his presentation. C. *sordellii* is an anaerobic organism that was initially isolated in 1937. The gram-positive rod forms spores and was traditionally believed to be a virulent form of C. *bifermentans*.

In one case of C. *sordellii* infection, a male 4 years of age broke his arm in a fall. Pain and marked swelling were noted with no fever, normal blood pressure and a rapid pulse. Cefazolin was administered intravenously and a volar fasciotomy was performed. Necrotic muscle and fascia were later revealed and tissue samples grew a culture of C. *sordellii*. The WBC count rose to 41,000 with increased hypotension, tachycardia and metabolic acidosis. The patient died within three days after the fall.

In another case of C. *sordellii* infection, a female 21 years of age had a vaginal laceration during natural childbirth. Perineal pain increased, the temperature was normal, blood pressure was low, the pulse was 132 and the WBC count was 67,000. Gentamicin and clindamycin were administered intravenously, a fasciotomy of the vulva was performed, and vancomycin was added. The WBC count rose to 123,000 post-operatively. Hypotension, metabolic acidosis and super-ventricular tachycardia developed with a pulse of 170. Copious amounts of intravenous fluids were administered, but the patient went into cardiac arrest and died. The tissue cultures grew *C. sordellii*.

A database search of reported *C. sordellii* infections yielded 28 reports due to postpartum or obstetrical/gynecological (OB/GYN) infections, MIAs, spontaneous abortions, injection drug use, trauma, surgical procedures or "other" causes. Of 41 patients 17 days to 95 years of age, 49% were males and 51% were females. The data review demonstrated that *C. sordellii* is a deadly disease for females due to postpartum and OB/GYN infections. The most significant factors in the cases were non-elevated temperatures, high WBC counts, hypotension, leukemoid reactions, hemoconcentration with a rising hematocrit, and non-*C. sordellii* organisms.

Autopsy findings of the cases showed local necrosis and acute inflammation; marked tissue or visceral edema; pericardial, pleural or peritoneal effusion; thrombosis of localized blood vessels; and neutrophil degeneration at margins of necrotic tissue. Potent exotoxins clearly play a role in the pathogenesis of *C. sordellii*. Investigations are underway focusing on mechanisms of the capillary leak syndrome and leukemoid reaction. These processes significantly contribute to both *C. sordellii* and *C. difficile*.

In a cell proliferation assay, HL-60 cells were utilized; *C. sordellii* toxins were collected from stationary phase cultures; ammonium sulfate precipitation was developed with isoelectric focusing; and fractions were created with different isoelectric points from 3-10. The cells were exposed to various fractions and were identified by flow cytometry. In an endothelial cell permeability assay, primary human umbilical vein endothelial cells were cultured on a membrane-lined insert to confluency. Permeability was measured by electrical resistance across the membrane. Toxins were added and resistance was measured over a 12 hour-period. A striking difference was seen in the degree of permeability of the endothelial cells and the rapidity of onset.

The investigation is also focusing on the innate immune recognition and response to *C. sordellii*. HEK-293 cells were transfected with genes for toll receptors 1, 2, 4 and 6 individually and collectively. The cells were also transfected with MD2, CD14 and ELAM-1-dependent luciferase reporter systems. Cytokines were measured from peripheral blood mononuclear cells stimulated in parallel. The data showed that toll receptor 4 was used exclusively by LPS and not by clostridia, the exception being *C. septicum*. Toll receptor 2 and a combination of toll receptors 2 and 6 were found to be optimal for the remainder of the *Clostridia* species. Receptors on immune cells that recognize *C. sordellii* in the absence of any acquired immunity were identified.

C. sordellii was found to be equally as potent as lipopolysaccharide (LPS) in terms of cytokine induction. The *C. sordellii* toxin crude preparation was a very potent inducer of IL-1β, but lethal toxin was not. Granulocyte macrophage-colony stimulating factor (GM-CSF) was induced by *C. sordellii* toxins, but was not produced by the lethal toxin. Interleukin-10 was produced to a greater extent by lethal toxin compared to the cruder preparation. The important pathogenic mechanism in *C. sordellii* is the diffuse capillary leak syndrome that appears to be related to direct toxin effects on endothelial cells. The leukemoid reaction appears to play a role in the synergistic interaction between GM-CSF and the ability of a *C. sordellii* toxin to stimulate proliferation of bone marrow progenitor cells.

The Pathophysiology of Mifepristone-Induced Septic Shock Due to *C. Sordellii*

Dr. Ralph Miech is an *Emeritus* Associate Professor in the Department of Molecular Pharmacology, Physiology and Biotechnology at Brown Medical School. He covered the following areas in his presentation. Mifepristone may have contributed to the deaths of four healthy women in California from septic shock due to *C. sordellii* infection following medical abortions. In all four cases, the women were <2 months pregnant, given a single dose of 200 mg of mifepristone orally, and self-administered 800 µg of misoprostol vaginally 24-48 hours later. All four women died within a five- to seven-day time period with clinical signs of shock, absence of fever, leukocytosis and hemoconcentration.

Most drugs are eliminated from the body in a few hours, but pharmacokinetic studies have shown that the long half-life of mifepristone is generally on the order of 20-30 hours. As a result, four to five days would be needed to remove 95% of the drug from the body. Other data have demonstrated that some humans have an unusually long half-life and would need 18 days to remove 95% of mifepristone. Mifepristone is principally removed from the body by metabolism.

Of six different metabolites of mifepristone that have been identified, some have retained biological activity as progesterone antagonists. However, further research is needed on the effects of these six metabolites on the innate immune system. *In vitro* studies with liver microsome enzymes have shown that the cytochrome P450-3A4 enzyme is primarily responsible for metabolizing mifepristone. Evidence also suggests that the enzyme can be inactivated during the metabolism of mifepristone and accounts for the relatively long biological half-life in humans.

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Mifepristone binds with high affinity to both progesterone and anti-glucocorticoid receptors and blocks cortisol receptors in peripheral tissues and the central nervous system. Blockade of negative feedback receptors in the hypothalamus results in increased serum levels of ACTH and cortisol. Experimental animal protocols have demonstrated that mifepristone produces a temporary drug-induced adrenalectomy. Mifepristone was originally developed as an anti-glucocorticoid for the treatment of Cushing's disease. The drug was later discovered to possess anti-progesterone activity and act as an abortive agent.

Mifepristone's anti-progesterone activity results in pharmacological actions on the pregnant uterus, including cervical ripening, ischemia of the decidua, necrosis of the products of conception, and sensitization of the myometrium to contraction by prostaglandins. *C. sordellii* and other *Clostridium* species have been found in the normal vaginal flora in 8%-18% of women. Macrophages, monocytes, neutrophils and endothelial cells serve as the first line of defense for a host to counter bacterial invasion of the interstitial space of uterine tissue. In the reported cases, mifepristone anti-glucocorticoid action initially impaired the proper functioning of the cells of the innate immune system within the pregnant uterus and ultimately led to a uterine infection with *C. sordellii*.

Lipoteichoic acid and peptidoglycan molecular components are unique to cell walls of anaerobic bacteria. These unique biochemical entities bind to and activate toll-like receptors on tissue macrophages. Toll-like receptors function as principal sensors of infection in mammals when activated and cause an outpouring of pro-inflammatory cytokines at the site of bacterial invasion. Tumor necrosis factor alpha and interleukins-1 and -6 are the principal pro-inflammatory cytokines that are synthesized and secreted by phagocytes.

When inflammation is properly controlled, invading bacteria are destroyed without tissue damage. However, *C. sordellii* can successfully establish an infection with the secretion of lethal toxin. Excessive pro-inflammatory cytokines can gain access to the systemic circulation if local reaction of pro-inflammatory cytokines is not controlled. Both of these events contribute to the etiology of septic shock and multiple organ dysfunction. The proper timing and amount of cortisol are crucial to maintaining control of the inflammatory response and preventing tissue damage.

Cortisol binds to intracellular glucocorticoid receptors and phagocytes to cause increased transcription of DNA. This process results in the synthesis and secretion of the interleukin-10 anti-inflammatory cytokine. Interleukin-10 suppresses the generation of excessive pro-inflammatory cytokines, tumor necrosis factor alpha, and interleukins-1 and -6 by cells of the innate immune system.

Animal experiments support the hypothesis that mifepristone can facilitate infection and lead to lethal septic shock. A study showed that a single dose of the drug administered to mifepristone-treated mice dramatically increased the mortality rate of polymicrobial septic shock nearly three-fold. Mifepristone may impair the innate immune system to delay proper removal of *C. sordellii* from the decidua and allow bacteria to secrete lethal toxin into the uterine interstitial fluid.

Phagocytes, endothelial cells and uterine cells allow entry of lethal toxin and prevent proper participation in defensive inflammatory responses of the innate immune system. Lethal toxin functions as an intracellular enzyme that catalyzes the glucosylization of G-proteins when internalized by uterine phagocytes and internal endothelial cells. G-proteins are molecular switches that activate or inhibit a multitude of vital biochemical cascades and genetic transcription functions for proper functioning of cells. Glucosylization causes G-proteins in uterine phagocytes to become useless in destroying bacteria.

Overall, mifepristone's anti-progesterone effects prepare the aborting uterus as an ideal bacterial culture for *C. sordellii* by causing ischemic decidua that leads to necrotic products of conception. Mifepristone's anti-glucopharmacologic actions disrupt the hypothalamic pituitary adrenal axis and interfere with the functioning of peripheral glucocorticoid receptors at a crucial time. This process results in a lack of control of the pro-inflammatory cytokine response and allows for the establishment of a nidus of infection with *C. sordellii* and localized secretion of lethal toxin.

Phagocytes in the decidua are permanently inactivated by lethal toxin and allow *C. sordellii* to multiply and secrete excess lethal toxin into the systemic circulation. The combination of lethal toxin and excess inflammatory cytokines in the systemic circulation can synergistically collaborate to produce clinical findings of rapid fulminating lethal shock syndrome that were the hallmark of the four cases in California.

Bacterial Toxin Repression of Nuclear Hormone Receptors: Host-Pathogen Hormone Interactions and Implications for Therapy

Dr. Esther Sternberg, of the NIH National Institute of Mental Health, covered the following areas in her presentation. Hormones have profound effects on host inflammatory and immune responses. Research conducted in 1989 showed that glucocorticoids and progesterone generally suppress inflammatory responses. *Clostridia* bacterial toxins partially repress glucocorticoid receptor transactivation. *Clostridia* bacterial toxins partially reverse dexamethasone suppression of TNFα production. Sub-pharmacological concentrations of mifepristone plus TcsL completely reverse the effects of dexamethasone suppression of TNFα production *in vitro*.

The priority in future research will be to determine if *in vitro* findings can translate to *in vivo* situations of shock. Emphasis should be placed on the time course after exposure to bacterial products; an individual's dose-response and exposure to hormones and drugs; prostaglandins or other drug interactions; and pregnancy and menstrual cycle hormone levels, receptor polymorphisms or mutations that may make some persons more susceptible to inhibitory effects of other factors blocking these receptors.

The published literature is increasingly demonstrating that glucocorticoid receptor polymorphisms or mutations in associated proteins necessary for the glucocorticoid receptor to function are prevalent in numerous autoimmune and inflammatory diseases. These polymorphisms and mutations may also play a role in enhanced inflammatory responses in certain individuals. Host factors, bacterial product interactions with the host, and immune and hormonal responses that interact with these factors must all be considered in future research to identify risk factors to prevent these occurrences.

Panel 1-Session 2 Discussion

The Panel 1-Session 2 presenters provided additional details about the clinical syndromes, pathophysiology and host factors of *C. sordellii* in response to questions and comments from the participants.

- Broad spectrum or focused antimicrobial agents should not be given for *C. sordellii* because this occurrence is still rare. Administering antimicrobial agents with activity against *C. sordellii* while initiating the medical termination should not be considered because multiple changes in the microecology of the patient would be provoked. For example, 10% of patients would immediately develop yeast infections and have changes in the GI flora.
- A hypothesis to link *C. difficile* and *C. sordellii* in the pregnant patient should be tested in animal models. For example, a pregnant woman would be more at risk for infection if progesterone is elevated and is found to be an equally important anti-inflammatory factor in *in vivo* studies

compared to *in vitro* studies. The patient may develop shock if certain bacteria producing these toxins generate no greater growth and toxins inhibit inflammatory responses that are intended to protect the host from bacteria.

- *C. sordellii* spores, microorganisms and other substances from the vagina are transported inside the uterus when the uterus contracts. These factors and prolonged bleeding during medical treatment are extremely important to consider during intravaginal administration of misoprostol. Denmark, Sweden and the Netherlands have developed nationalized medical systems and better tracking processes than the United States. Efforts should be made to review and collect epidemiologic data from these countries.
- *C. sordellii* cases have been reported in the literature, but the epidemiology has not been identified at this point because these serious infections are still rare. Speculations have been raised that *C. sordellii* infections may be attributed to an individual's predisposition, the actual agent used or the polymorphism for the P450 enzyme.

PANEL 2: SURVEILLANCE FOR DISEASE AND SOURCES OF INFECTION

The Panel 2 speakers made presentations to identify current and future surveillance needs and barriers to disease and sources of infection. The two Panel 2 presentations are outlined below.

Federal and International Initiatives

Dr. Clifford McDonald, of the CDC Division of Healthcare Quality Promotion, covered the following areas in his presentation. Most CDAD is acquired in healthcare facilities, but these infections are not nationally reportable and currently require alternative sources of national data to determine disease rates. CDC's National Hospital Discharge Survey showed that CDAD discharge diagnosis among U.S. hospital patients doubled between 2000-2003 and increased an additional 25% in 2004.

Other countries are also making efforts to survey CDAD in hospitals. In August 2004, Quebec instituted mandatory reporting of CDAD for acute care hospital cases, including cases with symptom onset ≤ 1 month post-discharge, major complications and death. Canada performed two national sentinel surveys in 1997 and 2005 to determine CDAD rates and also collected *C. difficile* isolates from facilities in 2005. In January 2004, England instituted mandatory reporting of CDAD among all patients $\geq$65 years of age for all healthcare facilities within individual national health system trusts.

CDC has taken several actions to prioritize and promote surveillance of HA-CDAD. Surveillance recommendations were developed and are currently being reviewed by external partners. The guidance will formally state CDC's communications on its web site and public presentations. Definitions and methods that should be used to report infections will be clearly outlined. The recommendations will be targeted to healthcare facilities and networks, state health departments and public reporting initiatives. All healthcare facilities are advised to conduct some type of surveillance.

CDC is using its EpiCenter hospital grantees to analyze surveillance methods and is also developing a CDAD surveillance component for inclusion in the National Healthcare Safety Network. A 2005 *MMWR* article featured reports of CA-CDAD among 23 generally healthy persons who had no recent exposure to healthcare facilities. Several of these individuals also had no recent antimicrobial use. An increase in CA-CDAD among persons who sought care at the VA Hospital in Atlanta, Georgia was also reported to CDC. PPIs appeared to increase the risk for CDAD in these patients.

A 2005 *MMWR* article described ten cases of pregnancy-associated CDAD from four states that resulted in severe disease and one death. CDC and the Emerging Infections Network of the Infectious Disease of Society of America are collaborating to actively investigate additional cases of pregnancy-associated-CDAD. Of 405 infectious disease clinicians who responded to a survey, 4% reported having seen cases and 6% were aware of cases in their respective communities. Of the 48 cases of pregnancy-associated CDAD reported through the survey, 29% occurred prior to delivery; 20% developed recurrent disease; three developed toxic megacolon; one resulted in fetal loss; and one resulted in maternal death.

Since 2000, CDAD outbreaks have been reported in food-producing animals, particularly neonatal pigs, beef and dairy calves. The strains infecting animals are genetically different from the most common human strains. The same PCR ribotype is causing recent outbreaks in both pigs and calves, but is not the traditional ribotype among human isolates. However, the epidemic animal strains share certain characteristics with the recently described human epidemic strain and may indicate increased virulence. Both the human and food animal epidemic strains carry the binary toxin and toxins A and B and have a deletion in the putative *tcdC* toxin regulatory gene.

The human epidemic strain has an 18-base pair *tcdC* deletion, while the food animal strain has a 39-base pair deletion.

CDC is aware of human CDAD cases that are caused by strains similar to animal epidemic strains. Pulsed-field gel electrophoresis genetic typing shows that animal and human isolates are at least 80% related. CDC's ongoing investigation indicates that five of seven human CDAD cases caused by animal epidemic strains fit a clinical picture typical. The cases are primarily occurring in healthcare facilities among older patients with significant co-morbid diseases. One death attributed to CDAD occurred in a younger patient without co-morbidities and may have been community-associated.

Disease occurring in food animal production facilities is primarily due to animal-to-animal transmission, but the existence of environmental sources or reservoirs for responsible stains is not known at this time. The transmission dynamics between food animals and humans are also unknown. CDC is partnering with FoodNet under the Emerging Infections Program (EIP) to investigate CA-CDAD and attempt to fill data gaps. Pilot studies were initiated to obtain isolates from community cases and perform cultures on retail meat samples.

For *C. sordellii*, CDC is actively investigating four additional (and previously unreported) cases of pregnancy-associated toxic shock-like syndrome. Of these four cases in which the pregnancy outcome was either medical or spontaneous abortion, all were <35 years of age, occurred since 2000, and three died. Of the five cases of toxic shock-like syndrome following medical abortion previously reported in the United States and Canada, all received mifepristone and intravaginal misoprostol 6-10 weeks gestation and developed a *C. sordellii* intrauterine infection. Of three additional medical abortion-related cases that CDC is still investigating, two occurred in the Western United States, at least one was known to have not taken mifepristone (but used laminaria and misoprostol instead), two were given intravaginal misoprostol, and two had *Clostridium perfringens* infections. CDC has been unable to confirm that a medical abortion was indeed performed for one of the patients.

Of the two previously reported cases of toxic shock-like syndrome following miscarriage, both occurred in the second trimester, both cases had a *C. sordellii* infection, and one had a *C. perfringens* infection. CDC's ongoing investigation of one additional case showed that *C. sordellii* recovered from blood did not contain genes encoding lethal toxin. Various passive case finding methods were used to notify CDC about the pregnancy-associated toxic shock-like syndrome cases, including FDA adverse events monitoring, reports from state health departments and academic partners, and the CDC Division of Reproductive Health Pregnancy Mortality Surveillance System.

The surveillance system prevents deaths by monitoring trends and identifying risk factors associated with deaths. However, clinical and pathology samples cannot be requested and identifiable information cannot be published due to privacy rules. CDC is collaborating with public health partners in California to identify additional cases of pregnancy-associated toxic shock-like syndrome. Death certificates of women 15- 44 years of age are being reviewed to identify anaerobic septicemia, TSS, inflammatory disease of female pelvic organs, or other indications of pregnancy-associated deaths. The death certificate review has identified 321 potential cases from 2000-2003.

CDC has tested a bank of isolates submitted over the past 30-40 years and confirmed that only a minority of clinical *C. sordellii* possess lethal toxin. These data show no increase in the number or proportion of isolates that are toxin-positive. Isolates that CDC genetically typed showed no evidence of epidemic *C. sordellii* strains. Only a few of these isolates appeared to be highly related to one another and no clustering was seen of toxin-positive versus toxin-negative strains. CDC acknowledges the critical need for further research on the epidemiologic sources and transmission dynamics of *C. sordellii.*

State Initiatives and Performance Characteristics of Optimal Surveillance Systems

Dr. Jeffrey Engel is the North Carolina State Epidemiologist in the North Carolina Division of Public Health. He covered the following areas in his presentation. The United States currently utilizes the passive Nationally Notifiable Disease System (NNDS) to report communicable diseases. Most states have laws that mandate physicians and laboratory directors to report communicable diseases. States also develop rules with a list of reportable diseases and specific mechanisms to submit reports.

North Carolina and several other states allow county health departments to be autonomous in reporting diseases, while other states institute regional reporting by health districts. Diseases are reported by event codes and extracted from confidential medical records. Public health departments are authorized to obtain all confidential records on any mandatory reportable disease in the state. However, disease reports can be discoverable in response to a Freedom of Information Act request or an individual's signed consent and release form. Public health departments also have authority to investigate non-reportable diseases and emerging infections, such as CDAD or *C. sordellii.*

One of three approaches can be taken to place emerging infections or diseases on the NNDS. The federal government can define an "emergency," such as severe acute respiratory syndrome or monkeypox. Other public health threats can be identified, such as pediatric influenza deaths or novel influenza virus. CDC and the Council of State and Territorial Epidemiologists can jointly develop consensus statements for case definitions. North Carolina and many other states require outbreaks to be reported to local health departments. However, hospitals in North Carolina are not mandated to report other diseases because information cannot be protected. As a result, HA infections are not reported to NNDS.

Two states are now taking actions to report CDAD. Connecticut initiated this effort to determine whether toxic strains were emerging in the community. A committee represented by hospitals, laboratories and community members approved the addition of CDAD to the state list of reportable diseases as of January 1, 2006. A descriptive epidemiologic program was piloted to analyze and evaluate trends of community-onset (CO) CDAD. Connecticut's case definition is the onset of illness while residing in the community and no contact with a healthcare or long-term care facility (LTCF) in the previous three months.

CDAD surveillance for the state of Connecticut is performed by infection control practitioners in 31 acute care hospitals and includes an intensive questionnaire, chart review and follow-up at a physician's office. Of the 86 cases investigated as of May 1, 2006, 39 were ruled out, 17 had actual CO-CDAD, and 30 are pending review. Connecticut is collaborating the CDC FoodNet program for the laboratory component of the CDAD surveillance system. CDC now receives cultures from 11 sites across the country and is seeking ten isolates of *C. difficile* organisms from Connecticut. Connecticut's most significant challenges in the CDAD surveillance system are resources and the storage of stool samples in laboratories while cases are being investigated.

Ohio initiated its CDAD surveillance system in response to concerns expressed by citizens and the media regarding CDAD outbreaks in healthcare facilities and a directive by the governor. Mandatory hospital and LTCF surveillance was established on January 1, 2006. At this time, ~200 acute care hospitals and 1,000 nursing homes report numerator data by week. Initial case reports of CDAD are also posted on the Ohio Department of Health web site. Ohio's previous public reports of HA-CDAD required >48 hours after admission, but the new version captures denominator data by bed or patient day.

By June 1, 2006, Ohio's public reports will reflect actual rates by patient day in acute care hospitals and rates by bed or occupied bed day in LTCFs. Risk adjustments will not be made for co-morbidities, age or other factors. Ohio has already benefited from the CDAD surveillance system with the establishment of a secure, web-based and statewide reporting tool. Moreover, the system provides an opportunity to educate healthcare facilities about appropriate antibiotic usage and infection control.

North Carolina requested an EpiAid from CDC in 2005 for assistance in investigating a marked increase of suspected CA-CDAD among veterans. The retrospective study covered the period of January 1-December 31, 2005 with a cohort of four VA Medical Centers, one tertiary care center and one regional hospital in the state. Of the 625 CDAD cases identified at this time, 48% were CO-CDAD and 24% were CA-CDAD. North Carolina's case definition was "no healthcare contact within two months." Of the 58 veterans in the study, the median age was 60½ years, 33% were on PPIs, 16% were on H2 blockers, 19% were on non-steroidal anti-inflammatory drugs, and 50% were on antibiotics. North Carolina is currently investigating all the patients in the study with no antimicrobial exposure.

Several characteristics are necessary for an ideal public health surveillance system. Stakeholders should be engaged in the evaluation. The surveillance system to be evaluated should be described. The evaluation design should be focused. Credible evidence regarding performance of the surveillance system should be gathered. Conclusions should be justified and stated and recommendations should be made. Evaluation findings and lessons learned should be used and shared. To optimize performance of a surveillance system, emphasis should be placed on simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive, representativeness, stability and timeliness.

Resources must be available for states to conduct surveillance. For example, Connecticut and ten other states are EIP grantees and receive federal funding to participate in the Active Bacterial Core Surveillance and FoodNet Programs and address emerging problems in the United States. The EIP sites will play a critical role in advancing state-level surveillance for *C. difficile* and other new infectious diseases in the future. EpiAids from CDC are free of charge and will continue to serve as a surveillance resource to states.

Panel 2 Discussion

The Panel 2 presenters provided additional details about the current and future surveillance needs and barriers to disease and sources of infection in response to questions and comments from the participants.

- Priorities for *C. difficile* disease surveillance at the federal level include continued emphasis on HA-CDAD; increased understanding of emerging forms of disease; the development of standardized surveillance guidelines and parameters; and stronger knowledge on CA-CDAD in special populations. Case finding will continue to serve as the most important priority at the federal level for *C. sordellii* disease.
- Priorities for *Clostridium* disease surveillance at the state level include new legislation for mandatory public reporting of HA infections; the establishment and monitoring of simple infection control interventions to reduce disease; and standardized methods for hospitals to share data.
- Electronic reporting through laboratory tests is the most promising method to conduct surveillance of *C. difficile* at both federal and state levels. A positive laboratory test on a liquid stool could serve as a surrogate for *C. difficile* disease. However, the period of risk of exposure to disease in a hospital must be clearly defined. For example, Canada conducts post-discharge surveillance of *C. difficile* over a four-week period and the European Union is considering a one-month period.
- CDC has found strains of *C. difficile* that are epidemic in food-producing animals and similar strains have been detected at a low rate in humans. Evidence has not been collected to demonstrate transmission through the food supply or any other means. CDC intends to actively investigate the impact of animal health, environmental factors and shared regulatory genes on human health in terms of *Clostridia*.
- CDC evaluates and investigates all reports of adverse events submitted by other countries on MIAs with mifepristone. CDC is extremely interested in collaborating with and collecting tissues from cases that occur in other countries. CDC has engaged other countries in dialogue about potential methods to strengthen case finding.
- CDC estimates that 400,000-500,000 CA-CDAD and HA-CDAD cases occurred based on 2004 data from the National Hospital Discharge Data Set, states, LTCFs and acute care facilities. Of persons with *C. difficile* infection, 1%-1.5% traditionally die from the disease. However, studies on the new strain in Canada show that 30-day mortality is more on the order of 6.8%.

mifepristone, misoprostol and other drugs with potential contributions to post-abortion infections.

- Increase knowledge and understanding of the microbiology and basic bacteriology of *C. difficile* and *C. sordellii*. Perform research on sporulation; mechanisms by which the organism germinates and initiates disease; nutrients on which the organism grows; and toxin regulation and genome sequence. Use these findings in killing the organism and neutralizing or suppressing the toxin.
- Conduct extremely cautious epidemiologic studies in appropriate settings among pregnant females to analyze *C. sordellii*, identify other postpartum infections, and develop better interventions for women colonized with *C. difficile* or *C. sordellii*.
- Ensure that active case finding is representative of pregnancy-associated deaths or severe illness regardless of whether an abortion was performed. Follow-up these cases with an intensive epidemiologic review to identify uncommon factors, laboratory diagnoses and factors other than cultures.
- Administer a survey or conduct a study among women in early and late pregnancy to determine potential changes over time. Compare women who first present for an obstetrical visit to those who present for an abortion. Apply findings between the two groups to identify differences in epidemiology, persons colonized with *C. difficile* or *C. sordellii*, and the number of toxigenic organisms.
- Perform research on the role of the media in communicating risk, assisting with case finding, and increasing the transparency of issues from both clinical provider and public health perspectives.
- Encourage CDC and FDA to jointly develop a consultation resource for emergency room physicians, OB/GYNs and primary care providers who have questions about potential *C. difficile* or *C. sordellii* cases. For example, practitioners could call a toll-free telephone number to receive accurate information and obtain support on reporting cases.
- Thoroughly review the published literature in developing the research agenda to strengthen understanding of and explore the possible causal relationship among mifepristone, medical abortions and *Clostridia* infections. Widely publish these findings for physicians to recognize, intervene and treat signs and symptoms of toxic shock-like syndrome early in the progression of disease. Provide clear guidance to clinicians on non-specific symptoms of TSS and appropriate clinical judgments on antibiotic treatment versus conservative or aggressive surgery.
- Perform research to identify effective methods to educate and communicate information about case finding and the prevention of

catastrophic outcomes from large clostridial toxins. Target these messages to emergency room physicians, primary care physicians and other non-infectious disease clinicians who will actually treat *C. difficile* or *C. sordellii* cases.

- Place emphasis on the role of large clostridial toxins in abdominal sepsis to measure toxin levels in peripheral blood.
- Educate women on postpartum infections and the potential consequences of pregnancy or MIAs.
- Determine whether federal agencies can focus on other diseases with a similar pathology or pathogenesis that are higher priorities than *C. difficile* or *C. sordellii* and can be translated into a useful animal model.
- Urge FDA to collaborate with France and other countries to enhance knowledge of specific drug use patterns and strengthen case finding.
- Clearly define, validate and use "severity of disease" in the research agenda to better identify and categorize *C. difficile* sources of disease, particularly patients at high risk of complications or fatal outcomes who need more aggressive management. Widely communicate the severity of disease case definition to identify patients as early as possible in the progression of disease.
- Encourage pathologists to perform microbiologic research on fresh tissues to identify cases of *C. sordellii.*
- Conduct studies and develop better genetic tools on the basic physiology of *C. difficile*, particularly spore formation, virulence factors, spore germination and the genome sequence.
- Partner with the National Association of Public Health Veterinarians and the U.S. Department of Agriculture to determine the role of zoonosis in *C. difficile* disease, identify the contribution of spores in the human food chain, and collect isolates from human CA-CDAD cases.
- Improve and utilize clinical scoring systems early in the progression of disease to predict persons with potentially poor outcomes, those who will fail metronidazole therapy and other elements. Validate the clinical scoring system prospectively.
- Develop a solid and sensitive toxin assay in blood or serum to measure organs other than the colon that play a role in severe *C. difficile* disease and toxicity.
- Partner with the American Institute of Architects of Healthcare Design in designing spaces in hospitals to increase hand washing among healthcare providers.

Summary of Key Findings

Dr. John Bartlett is the Chief of the Division of Infectious Diseases at John Hopkins University. His summary of the key findings and recommendations made during the workshop is outlined below.

- Perform research on overlapping areas between *C. difficile* and *C. sordellii*, such as the regulation and mechanism of toxins, the role of sporulation, virulence factors, and the role of flora in controlling the organism.
- Conduct sentinel studies to collect more data on *C. difficile*, particularly in the areas of non-antibiotic use and the new epidemic strain.
- Use the tissue culture assay and common antigen as a screening test until the rapid, inexpensive and sensitive PCR technology that will identify toxin B is released in the near future. Advance efforts to release the NAP1 test that will provide information about the new strain.
- Increase the practice of culturing stool in the United States or develop and use binary toxin, deletion or another non-culture-based method to recognize *C. difficile* strains.
- Clearly determine whether vancomycin or metronidazole should be used to treat *C. difficile*. Clearly distinguish between agents that are needed to treat acute versus intermittent disease. Acknowledge that vancomycin is viewed as the "perfect drug" in treating acute disease.
- Focus new drug development on intermittent and recurrent *C. difficile* disease for patients who are unable to take oral therapy due to the significant morbidity in this population.
- Review cases of CA-CDAD and antibiotic exposures to determine the number of cases hospitals were justified in using antibiotics.
- Develop guidelines on the use of drugs that do not drive *C. difficile* disease. Highlight the significant differences among the broad-spectrum clindamycin, cephalosporin and fluoroquinolone classes of drugs.
- Launch a national initiative to add HA-CDAD as a reportable disease.
- Strongly urge public health to partner with the VA because this agency maintains the best and largest electronic medical record system in the world. Utilize this valuable resource to obtain rapid answers on *C. difficile* from data that were previously collected.
- Improve surveillance systems of *C. sordellii* to increase capacity in detecting the infection.

- Revitalize laboratory interest in the area of anaerobic cultures to enhance capacity to rapidly and inexpensively culture *C. difficile*, *C. sordellii* or other histotoxic *Clostridia*.

Closing Session

Dr. Leslye Johnson is the Chief of the Enteric and Hepatic Diseases Branch at the NIH National Institute of Allergy and Infectious Diseases. She made the following remarks to conclude the workshop. The expert panel and members of the audience are to be commended in providing CDC, FDA and NIH with up-to-date findings, interesting hypotheses, valuable recommendations, and solid future directions in developing a research agenda for complex issues related to *C. difficile* and *C. sordellii*. The research agenda will serve as a living document that will be modified over time as new science is produced.

The organisms emphasize the critical need for multi-disciplinary research. Most notably, NIH encourages investigators to apply for R01 grants and funding for small developmental studies because *C. difficile* and *C. sordellii* are now viewed as priorities throughout the agency. Federal attention will continue to be paid to these issues through CDC's external partnerships and ongoing interagency collaborations among CDC, FDA and NIH.

Dr. Johnson confirmed that NIH is extremely encouraged about clinical trials for *C. difficile* that are underway to identify effective therapeutic and preventive approaches. She emphasized that the ongoing research will provide an opportunity for public/private partnerships between NIH and other federal agencies to advance the field as quickly as possible.

ATTACHMENT 2

Choice of and Satisfaction with Methods of Medical And Surgical Abortion Among U.S. Clinic Patients

By S. Marie Harvey, Linda J. Beckman and Sarah J. Satre

Context: *Abortion induced by drugs is now a viable alternative to surgically induced abortion for U.S. women. Women's willingness to use these new methods of medical abortion hinges on the extent to which they prove acceptable, however.*

Methods: *Among 304 women participating in a clinical trial of medical abortion, 186 received a methotrexate-induced abortion and 118 were offered the option of a medical abortion but chose a surgical procedure instead. Study participants completed self-administered questionnaires before the abortion and again at a follow-up visit.*

Results: *Women in the medical and surgical abortion groups did not differ significantly with regard to demographic and other background characteristics: Their mean age was about 27, more than two-thirds were white, and three-quarters were unmarried and worked either part-time or full-time. However, women's ratings of seven attributes of abortion methods were significant predictors of choosing a medical abortion: Women were more likely to choose medical abortion if they placed greater importance on a method that was nonsurgical, one that resembled a miscarriage or one that could take place at home (odds ratios, 2.0–3.3). Conversely, women were less likely to choose medical abortion if they valued methods that were quick, that did not involve painful cramping or seeing blood or blood clots and that needed a doctor or nurse to be present (odds ratios, 0.3–0.5). Compared with those who had a surgical abortion, women who had a methotrexate-induced abortion expected more bleeding (mean scores, 3.5 vs. 3.1) and reported more pain (3.4 vs. 2.9), heavier bleeding (3.4 vs. 2.5) and bleeding of longer duration (3.3 vs. 2.6). The overwhelming majority of women in the medical and surgical abortion groups reported that they were either very or somewhat satisfied with their abortion method (81% and 82%, respectively), would recommend it to others (82% and 78%) and would choose the method again (89% and 93%).*

Conclusions: *Factors affecting the choice of abortion method appear to be numerous and complex. Providers need to be sensitive to differences in women's values and life circumstances when counseling them about an abortion method. In particular, providers should incorporate into their counseling sessions what women need to know about the characteristics of abortion methods and help women to identify what is the best option for them.*

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In the United States, women seeking to terminate an early pregnancy now have a choice between medical and surgical abortion procedures. The two major drugs currently being used to induce abortion are mifepristone and methotrexate (both used in conjunction with the mild prostaglandin misoprostol). Medical abortion induced with mifepristone followed by misoprostol has been used extensively in Europe and China. However, only recently has this option become available to U.S. women. The Food and Drug Administration (FDA) gave final approval to release mifepristone for use as an abortifacient on September 28, 2000, after 12 years of political struggle. In the early 1990s, prior to the approval of mifepristone, medical researchers also began to explore the use of methotrexate to induce abortion.[1] Methotrexate had already received FDA approval in 1953 for the treatment of cancer; thus, physicians could prescribe it legally as an abortifacient, even though it had not been approved by the FDA for that purpose.

The availability of medical abortifacients promises to increase U.S. women's access to abortion, but this will happen only if women are willing to use them and if they find such drugs acceptable. Acceptability among consumers is particularly important because the success of medical abortion depends on women's willingness to complete the regimen at home and to wait for the drugs to take action. In addition, information about women who choose this option, and how they differ from women who select the more traditional surgical procedure, is important to health care providers planning to offer medical abortion services.

Several studies conducted outside the United States have documented that women find medical abortion acceptable. Although the published studies of first-trimester medical abortion are diverse in research designs, their findings are quite consistent: Most women who had a first-trimester medical abortion were satisfied with the procedure, would choose it again if they needed to terminate another pregnancy and would recommend it to their friends.[2]

Only a handful of studies have explored the acceptability of medical abortion among U.S. women.[3] These studies, like those conducted in Europe and Asia, document high levels of acceptability among women who chose and used medical abortion for first-trimester abortion. Although these descriptive studies indicate that medical abortion is acceptable to American women, no studies to date have directly compared the acceptability of medical abortion to that of the current standard therapy, suction curettage abortion. Moreover, no studies have examined factors associated with the selection of medical versus surgical procedures among women in the United States.

Our overall purpose in this article was to compare women who chose methotrexate-induced abortion with those who selected suction curettage abortion regarding their experience and level of satisfaction with the abortion procedure. Our specific objectives were to: identify factors associated with the choice of abortion method; compare the two groups with regard to anticipated and actual experience

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S. Marie Harvey is director of research, Center for the Study of Women in Society, University of Oregon, Eugene, OR. Linda J. Beckman is professor of health psychology, California School of Professional Psychology, Alliant University, Los Angeles. Sarah J. Satre is research associate, Applied Research Northwest, Bellingham, WA. The authors are grateful to the site coordinators and staff at the participating Planned Parenthood clinics, especially Sue Ferden in Iowa, Madge Armstrong in Pennsylvania, Evonne Morici and Rebecca Whiteman in California, Jini Tanenhaus in New York and Vicki Jacobs in Arizona. Funding for the research described in this article was provided by grants from The John Merck Fund and the Education Foundation of America to the Public Health Institute; the authors heartily thank them for their generous support. Finally, the authors thank the women who took the time to share their perceptions and experiences.

(pain, anxiety and bleeding) with their abortion method; determine whether women who have medical abortions are more or less satisfied than women who have surgical abortions; and identify factors associated with women's satisfaction with their chosen abortion method.

Methods

Participants

This acceptability study was conducted in conjunction with the Planned Parenthood Federation of America (PPFA) clinical trial to evaluate the medical abortion experience for women and determine the effectiveness of methotrexate and misoprostol for early abortions. Our sample includes 186 women who had methotrexate-induced abortions while enrolled in the PPFA clinical trial at clinics in Des Moines; New York City; Phoenix; York, Pennsylvania; and Walnut Creek, California. We compare these women with 118 who were eligible for the clinical trial and were offered the option of a medical abortion, but chose the surgical procedure instead.

In the protocol used by PPFA, methotrexate was administered in the form of an injection during a clinic visit. Women were then given two doses of misoprostol (eight tablets, 200 milligrams each) to take at home, with instructions to insert one dose vaginally 4–6 days after the injection of methotrexate. If the abortion did not occur within 48 hours of insertion, they were to insert a second dose. A return visit to the clinic was required within 14–16 days after the initial injection.[4]

Although the majority of the surgical procedures were performed using electrical vacuum aspiration, 10% were done with manual vacuum aspiration. All surgical patients were scheduled to return for a follow-up visit 2–4 weeks after the procedure.

Between September 1997 and July 1998, clinic personnel at participating PPFA affiliates recruited all women who were 18 years of age or older and who met the eligibility requirements for the methotrexate clinical trial.* After the women had been counseled on abortion method options and had chosen either medical or surgical abortion, they were given written information about the acceptability study. Clinic staff explained to the women that their participation was completely voluntary and would not affect the care they received. The women were given time to look over the materials and trained clinic staff answered their questions. If a woman expressed interest, she was asked to give written consent for the acceptability study, and she was given brief instructions on how to complete the questionnaires.

Of the 368 eligible women asked to participate, 304 (83%) consented and completed the initial questionnaire (81% of the surgical group and 86% of the medical group). Women who agreed to participate were compared with those who refused on three demographic characteristics: age, ethnicity and education. Although the two groups did not differ significantly by age or ethnicity, women who participated in the study reported significantly higher levels of education than did nonparticipants ($p<.05$).

Among the 304 participants, 255 (84%) completed the follow-up questionnaire. The follow-up rate was significantly higher among women who had undergone medical abortion than among those who had had a surgical abortion (89% vs. 76%, $\chi^2=8.26$, $p<.01$).

Data Collection

Data were collected at two stages, using pretested, self-administered questionnaires. Women completed the initial questionnaire after they had chosen their abortion method but before the injection was given or the surgical procedure was performed. This instrument collected background information and data on the following topics: the abortion method chosen; women's expectations about the method chosen with regard to pain, anxiety and bleeding; and the relative importance of different method characteristics in women's decision-making. Clinic staff verified the abortion methods reported by the women.

Participants completed the second questionnaire during or after their follow-up visit to the clinic. Data collected in this questionnaire included women's experience with the abortion method, their degree of satisfaction with the method, whether they would choose the method again and whether they would recommend the method to friends. The surgical patients were required to complete the questionnaire within four weeks of the procedure; approximately 90% did so at their two-week follow-up visit. Medical patients were required to complete the questionnaire no more than two weeks after clinic staff confirmed that the abortion was complete; the vast majority did so during the visit at which the abortion was confirmed to be complete. Three-fourths of the women had confirmed complete abortions within 20 days after the administration of methotrexate (median, 15 days). Thus, approximately 60% of the medical patients completed the follow-up questionnaire within two weeks and 80% within three weeks of administration of methotrexate.

Measures

To determine the characteristics that women value in an abortion method, in the initial questionnaire we asked participants to rate the importance of 21 characteristics "when choosing between surgical and medical abortion." Participants recorded their responses on a five-point Likert scale ranging from a value of 1 for "not important" to a value of 5 for "extremely important."

On the initial questionnaire, women were asked about their expectations regarding four aspects of their abortion procedure: pain, anxiety, amount of bleeding and length of bleeding. At follow-up, they were asked about their actual experiences based on the same four items. Women rated each item on a five-point Likert scale. For the first three characteristics, scale points ranged from "none" (1) to "extreme" (5). For the length of bleeding, possible responses were 1–3 days (1), 4–6 days (2), 7–9 days (3), 10–12 days (4) and 13 or more days (5). We used identical scale points for expectations and experiences, but the wording of items differed slightly (e.g., "How much pain do you think you will have?" in the initial questionnaire, versus "How much pain did you have?" in the follow-up questionnaire.)

Finally, we assessed women's satisfaction with their chosen abortion method using responses to three questions from the follow-up survey. The first asked, "How satisfied were you with your abortion method?" Participants were asked to indicate if they were "very satisfied," "satisfied," "neutral," "dissatisfied" or "very dissatisfied." The second question asked women whether they would recommend

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*Women were eligible to enroll if their pregnancy was no more than 49 days of gestation. Vaginal ultrasound was required. Clinicians used the fetal embryonic pole (if present) to determine gestational age; otherwise, they used the diameter of the gestational sac. If the embryonic pole was longer than 10mm, the woman could not enroll. A gestational sac did not need to be present for a woman to be enrolled, but if a sac was not present, a serum beta-HCG was performed. If the beta-HCG was less than 2,000 mIU/ml and if the woman did not have symptoms suggestive of ectopic pregnancy, she could enroll. Women with a hematocrit of less than 30% were excluded. Rh-negative women received minidose Rh immune globin on the day of methotrexate administration. Although women younger than 18 were eligible to enroll in the clinical trial if they had parental consent, all participants in the acceptability study were required to be 18 or older. (Source: see Borgatta L et al., 2000, reference 3.)

Table 1. Mean values, percentage distribution of abortion patients, by selected characteristics, and percentages with certain characteristics, all according to abortion method chosen

Characteristic	Total (N=304)	Surgical (N=118)	Medical (N=186)
Age (mean)	27.5	27.2	27.6
Ethnicity			
Black	12.4	8.7	14.7
Asian/Pacific Islander	3.7	3.5	3.8
Hispanic/Latina	11.0	8.7	12.5
White non-Hispanic	68.2	73.0	65.2
Mixed ethnicity/other	4.7	6.1	3.8
Education			
≤high school	23.1	26.2	21.0
Some college	41.4	45.8	38.7
Completed college/ some graduate ed.	35.5	27.9	40.3
Marital status			
Married	23.8	21.2	25.4
Not married	76.2	78.8	74.6
Employment status			
Does not work outside home	22.6	21.2	23.5
Works full-time	53.8	56.8	51.9
Works part-time	23.6	22.0	24.6
Parity			
0	48.5	49.6	47.8
≥1	51.5	50.4	52.2
% ever miscarried	20.5	18.6	21.6
% ever had an abortion	47.4	42.4	50.5
Comfort with decision to have an abortion			
Very comfortable	44.2	42.2	45.4
Somewhat comfortable	40.2	39.7	40.5
Somewhat uncomfortable	12.3	15.5	10.3
Very uncomfortable	3.3	2.6	3.8
% ever raped/ sexually abused	22.1	19.8	23.5

their abortion method to a friend. Women could respond by checking "definitely yes," "probably yes," "don't know," "probably no" or "definitely no." Also, women were asked which method they would choose if they were to have another abortion—surgical abortion or medical abortion with methotrexate and misoprostol.

Analytic Approach

We compared categorical variables using chi-square analysis, and continuous variables using either a t-test or a paired t-test (the latter for within-group comparisons). We conducted bivariate analyses to examine the association between abortion method choice and factors hypothesized to be relevant to this choice. Because of the large number of comparisons, we set the significance level for the bivariate analyses at p<.01. We then performed a logistic regression analysis to determine predictors of medical abortion selection, using only variables that were significant in the bivariate analyses. We also conducted bivariate analyses for medical and surgical abortion patients separately to examine the association between satisfaction with abortion and factors hypothesized to influence satisfaction.

Results

Participant Characteristics

Women in the medical and surgical abortion groups did not differ significantly with regard to any of the demographic characteristics examined (Table 1). Ages of participants in both groups ranged from 18 to 45; the mean age was 27.5 years. More than two-thirds of the women were non-Hispanic white, 12% were black and 11% were Hispanic or Latina. More women in the medical group (40%) than in the surgical group (28%) had completed college, although this difference was not statistically significant. Three-fourths of the participants were single and had jobs outside the home.

The two groups were also similar with regard to other background variables. Half of the participants (52%) reported a previous birth. One in five women had experienced a miscarriage (20%), and almost half (47%) had experienced a previous surgical abortion—although this proportion was somewhat greater in the medical abortion group (51%) than in the surgical abortion group (42%). Most women (84%) reported feeling very comfortable or somewhat comfortable with their decision to have an abortion. More than one-fifth of all participants (22%) reported having been raped, sexually abused or forced to have sex at some time in their lives.

Method Attributes and Method Choice

Women who chose medical abortion differed significantly from those who selected surgical abortion in their ratings of 14 of the 21 attributes (Table 2). Surgical abortion patients gave significantly greater importance than medical abortion patients did to 10 attributes: The procedure is over with quickly (4.6 vs. 4.0); it does not have side effects such as nausea, headache and diarrhea (3.8 vs. 3.2); it does not cause heavy bleeding (3.6 vs. 2.9); the patient does not see blood (3.0 vs. 1.9); the procedure does not cause cramping (3.6 vs. 2.5); it does not lead to bleeding for longer than seven days (3.5 vs. 2.9); it is a technique that has been used for a long time (3.9 vs. 3.1); it takes only a few visits (3.8 vs. 3.4); a doctor or nurse is present (4.1 vs. 2.8); and the patient knows where and when the abortion is taking place (3.9 vs. 3.4).

In contrast, medical abortion patients gave four attributes significantly greater importance than did surgical abortion patients: The procedure does not involve surgery (4.2 vs. 3.1), it takes place in the privacy of home (3.9 vs. 2.3), it does not involve surgical instruments (3.9 vs. 2.6) and it is like a natural miscarriage (3.9 vs. 2.6).

We included these 14 attribute ratings in a logistic regression model as predictors of choosing a medical abortion. The results of the logistic regression reveal that seven attributes were significant predictors of choosing medical abortion (Table 3). Women who placed greater importance on a method that did not involve surgery (odds ratio, 2.7), that allowed the abortion to take place at home (odds ratio, 2.0) and that resembled a natural miscarriage (odds ratio, 3.3) were more likely to choose medical abortion. Conversely, women were less likely to choose medical abortion if they valued a method that was quick (odds ratio, 0.3), that did not require the patient to see blood or blood clots (odds ratio, 0.5), that did not involve painful cramping for more than an hour (odds ratio, 0.5) and that was performed under a doctor's or nurse's supervision (odds ratio, 0.3). The regression model correctly classified 93% of the total sample,

Table 2. Mean rating of importance of attributes of abortion methods, by method chosen

Attribute	Surgical (N=118)	Medical (N=186)
Is very effective	4.6	4.5
Can be used very early in pregnancy	4.3	4.5
Lets you have the abortion over with quickly	4.6	4.0**
Doesn't have side effects like nausea, headache and diarrhea	3.8	3.2**
Doesn't involve heavy bleeding	3.6	2.9**
Hardly ever causes major health problems (infection, tearing the uterus)	4.5	4.5
Doesn't involve surgery	3.1	4.2**
Lets you have an abortion without people you are close to finding out about it	3.9	3.9
Lets you have the abortion in the privacy of your home	2.3	3.9**
Can be used later in pregnancy (after 9 weeks)	2.5	2.5
Doesn't involve seeing the blood and blood clots during the abortion	3.0	1.9**
Doesn't involve painful cramping for more than an hour	3.6	2.5**
Doesn't involve bleeding longer than 7 days	3.5	2.9**
Has been used for abortion for a long time	3.9	3.1**
Takes only one or two office visits	3.8	3.4**
Has a doctor or nurse around during the abortion	4.1	2.8**
Lets you have control during the abortion	3.4	3.5
Doesn't involve surgical instruments being inside you	2.6	3.9**
Lets you know where and when the abortion is going to happen	3.9	3.4**
Is like a natural miscarriage	2.6	3.9**
Is inexpensive	3.3	3.5

**Difference is significant at p<.01, t-test. ***Difference is significant at p<.001, t-test. *Note:* Responses were recorded on a five-point Likert scale, with 1=not important; 2=slightly important; 3=moderately important; 4=very important; and 5=extremely important.

including 96% of those who chose the medical procedure and 87% of those who chose surgical abortion (not shown).

Expectations and Experiences

Women who had chosen a medical abortion expected more bleeding than women who had chosen surgery (Table 4); otherwise, the two groups were similar in their expectations. When rating their actual experience, women who had undergone a medical abortion reported greater pain and heavier and more prolonged bleeding than did women who had had a surgical abortion.

Paired t-test comparisons were performed to evaluate how well women's abortion experiences matched their expectations. Women who had medical abortions experienced significantly more pain (mean of 3.4 compared with 3.2, p<.01) and bled longer (mean of 3.3 compared with 2.7, p<.001) than they had expected. Women who had surgical abortions experienced significantly less bleeding than they had expected (mean of 2.5 compared with 3.1, p<.001).

Acceptability of Abortion Method

Both methods were highly acceptable. Nearly half (48%) of the women who had participated in the clinical trial were very satisfied with their methotrexate-induced abortion. Another 33% reported that they were somewhat satisfied. Similar percentages of women who had had surgical abortions reported that they were very satisfied (43%) or somewhat satisfied (39%) with their abortion method (p=.64). The majority of participants reported that they would recommend the method they had experienced to a friend (82% of women in the medical group and 78% of those in the surgical group, p=.45). Similarly, 89% of the women in the medical group and 93% of those in the surgical group stated that they would select the same abortion method if they had to terminate another pregnancy (p=.33).

We compared women in the medical cohort who reported that they were satisfied or very satisfied (81%) with their abortion procedure with those who were neutral, dissatisfied or very dissatisfied regarding factors hypothesized to influence satisfaction. The 10 variables examined in these bivariate analyses included previous experience with surgical abortion, failure of the medical abortion procedure, four measures of the experience of abortion (anxiety, pain, amount of bleeding and duration of bleeding) and four measures of the difference between expectations and experience (anxiety, pain, amount of bleeding and duration of bleeding). The latter four measures were calculated by subtracting the expectation rating from the experience rating for each item. Among medical abortion patients, women who were satisfied or very satisfied did not differ from other women on any of these variables.

Women in the surgical cohort who reported that they were satisfied or very satisfied (82%) with their abortion procedure were compared with those who were neutral, dissatisfied or very dissatisfied with regard to the same factors described above (with the exception of procedure failure). Surgical patients in the dissatisfied group reported experiencing higher levels of anxiety (p<.01) compared with the satisfied group, but the two groups did not differ according to any other factors.

Table 3. Odds ratios (and 95% confidence intervals) from multiple logistic model predicting characteristics associated with choice of medical abortion

Characteristic	Odds ratio
Lets you have the abortion over with quickly	0.32** (0.15, 0.69)
Doesn't have side effects like nausea, headache and diarrhea	1.08 (0.54, 2.18)
Doesn't involve heavy bleeding	0.74 (0.35, 1.57)
Doesn't involve surgery	2.72** (1.46, 5.07)
Lets you have the abortion in the privacy of your home	2.03** (1.25, 3.30)
Doesn't involve seeing the blood and blood clots during the abortion	0.46** (0.26, 0.82)
Doesn't involve painful cramping for more than an hour	0.46* (0.22, 0.97)
Doesn't involve bleeding longer than 7 days	1.83 (0.88, 3.82)
Has been used for abortion for a long time	0.95 (0.51, 1.78)
Takes only one or two office visits	1.39 (0.77, 2.52)
Has a doctor or nurse around during the abortion	0.34*** (0.19, 0.61)
Doesn't involve surgical instruments being inside you	1.04 (0.53, 2.03)
Lets you know where and when the abortion is going to happen	0.43 (0.22, 0.83)
Is like a natural miscarriage	3.25*** (1.74, 6.06)
Model chi-square (d.f.)	*249.62 (14)*
-2 log likelihood function	*130.44*

*Significant at p<.05. **Significant at p<.01. ***Significant at p<.001. *Note:* Dependent variable is coded: choice of medical procedure=1; choice of surgical procedure=0.

Discussion

It is noteworthy that women's choice of method was not related to demographic characteristics, to prior experience with miscarriage, abortion or sexual abuse, or to level of comfort with the decision to have an abortion. These findings are supported by other studies which have not found demographic characteristics to be predictive of choice of method.[5] However, they appear to contradict some of the attitudes and observations of medical abortion providers documented in our previous study.[6] According to preliminary data from that study, many providers believed that women were better candidates for medical abortion or more likely to choose the method if they were older, more educated, of higher socioeconomic status and able to speak English.

Because the range of demographic and other characteristics of women in this sample is limited, additional research is warranted. However, our findings suggest that reproductive health providers and counselors need to reexamine their assumptions and recognize that factors affecting method choice are numerous and complex.

Women's preferences regarding abortion method characteristics were significant predictors of the abortion method that they chose. This finding underscores the fact that women have different values and life circumstances that may influence their choice of abortion methods. Providers need to be aware of and sensitive to such differences when counseling women about choice of methods.

Women who had methotrexate-induced abortions reported significantly greater pain, more bleeding and longer duration of bleeding than did women who had surgical abortions. This finding is consistent with a previous study documenting heavier and more prolonged bleeding among patients having mifepristone-induced abortions than among those who had surgical abortions.[7] Despite the greater discomfort and inconvenience associated

Table 4. Mean scores for expectations and experiences, by type of abortion procedure, according to component of abortion experience

Component	Expectations		Experiences	
	Medical (N=186)	Surgical (N=118)	Medical (N=165)	Surgical (N=90)
Pain†	3.2	3.1	3.4	2.9***
Anxiety†	3.0	3.1	3.0	2.9
Bleeding amount†	3.5	3.1***	3.4	2.5***
Duration of bleeding‡	2.7	2.6	3.3	2.6***

***Difference is significant at p<.001. †Mean score: 1, none; 2, slight; 3, moderate; 4, high; 5, extreme. ‡Mean score: 1, 1 to 3 days; 2, 4 to 6 days; 3, 7 to 9 days; 4, 10 to 12 days; 5, ≥13 days.

with medical abortion, the overwhelming majority of women in both groups reported that they were satisfied with their method, would recommend it to others and would choose the method again.

Our findings highlight the importance of abortion education and counseling. All women need to be knowledgeable about the characteristics of abortion methods and understand how their own values, experiences and life situations can help them to identify the best option. In addition to providing objective information about the methods (e.g., a medical abortion may involve more pain and heavier bleeding for a longer duration), providers should assist women in assessing their degree of comfort with having a surgical procedure, with seeing blood and tissue, and with experiencing an abortion without medical personnel being present. They should also determine whether a woman prefers an abortion that is completed quickly, that takes place in the privacy of her home or that resembles a natural miscarriage. By incorporating these issues into their counseling sessions, providers will assist women to make more informed choices among abortion methods.

Our sample of medical abortion patients was limited to women who had used methotrexate. No studies to date have contrasted the experiences and satisfaction of women who obtain methotrexate-induced abortions with those of women who get mifepristone-induced abortions. However, previous studies of both patients and providers indicate that women may prefer mifepristone abortions because they take less time.[8] It is therefore likely that mifepristone will become the drug of choice for medical abortions among women in the United States.

Because the characteristics of and procedures for these two types of medical abortion are quite similar, findings from this study can be applied to mifepristone-induced abortions, and perhaps even to new drug-induced methods still under development. However, research is still needed to evaluate women's experience with different types of drug-induced abortions, as well as their experience with mifepristone abortions versus surgical procedures.

Our sample may have limited generalizability. As previously mentioned, the women in our study sample were enrolled in a clinical trial. It is possible that early adopters of a new technology may differ from those who choose a method after it has become more established and familiar. Attitudes about newness and risk-taking may be important for both method choice and satisfaction.[9] Additionally, although response and retention rates were fairly high, women who enrolled in and completed our study may have differed from those who did not. Finally, because our sample was small and fairly homogeneous, our findings may not be generalizable to women from different racial and ethnic groups.

Our findings underscore the importance of expanding women's access to medical abortion. It is important to note that women were satisfied with whichever method they chose—medical or surgical. Previous studies have found that choice is associated with higher levels of satisfaction, regardless of the method chosen.[10] Giving women a choice among abortion methods should therefore increase their overall level of satisfaction with abortion methods and services. Facilities currently offering only surgical abortion should expand their services to include medical abortion, and health providers, policymakers and advocates should continue their efforts to make medical abortion available to all women in the United States.

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ATTACHMENT 3

U.S. Food and Drug Administration

OFFICE OF WOMEN'S HEALTH

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About the Office of Women's Health

About the FDA and Its Office of Women's Health

The U.S. Food and Drug Administration is the U.S. government agency that oversees most foods and medical products. Its job is to make sure that:

- food is safe, healthy, and clean
- medicines and medical devices are reasonably safe and effective
- cosmetic products are safe
- animal foods and drugs are safe
- food and medical products have proper labels

Our Mission

The U.S. Food and Drug Administration's Office of Women's Health (OWH) serves as a champion for women's health both within and outside the agency. To achieve its goals, OWH:

- Ensures that FDA functions, both regulatory and oversight, remain gender sensitive and responsive;
- Works to correct any identified gender disparities in drug, device and biologics testing, and regulation policy;
- Monitors progress of priority women's health initiatives within FDA;
- Promotes an integrative and interactive approach regarding women's health issues across all the organizational components of the FDA; and
- Forms partnerships with government and non-government entities, including consumer groups, health advocates, professional organizations, and industry, to promote FDA's women's health objectives.

Our Director

Kathleen Uhl, M.D., Assistant Commissioner for Women's Health
Phone: 301-827-0350
Fax: 301-827-0926

Reports

- Progress Report: "10 Years and Beyond" [PDF 496KB] *(March 2006)*
- Protecting and Advancing the Health of Women, a Congressional Briefing by the OWH director *(May 18, 2005)*

Other FDA Links

In its role as part of the Office of the Commissioner, the OWH supports and provides input to all FDA offices. The FDA is organized into centers that are responsible for different types of products, and most have programs and initiatives that support women's health. These centers include:

- Center for Food Safety and Applied Nutrition
- Center for Drug Evaluation and Research
- Center for Devices and Radiological Health

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FDA Office of Women's Health

Attachment 4

United States Government Accountability Office

GAO

Report to Congressional Requesters

November 2005

FOOD AND DRUG ADMINISTRATION

Decision Process to Deny Initial Application for Over-the-Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual

GAO

Accountability * Integrity * Reliability

GAO-06-109

GAO
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Highlights

Highlights of GAO-06-109, a report to congressional requesters

November 2005

FOOD AND DRUG ADMINISTRATION

Decision Process to Deny Initial Application for Over-the-Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual

Why GAO Did This Study

In April 2003, Women's Capital Corporation submitted an application to the Food and Drug Administration (FDA) requesting the marketing status of its emergency contraceptive pill (ECP), Plan B, be switched from prescription to over-the-counter (OTC). ECPs can be used to prevent an unintended pregnancy when contraception fails or after unprotected intercourse, including cases of sexual assault. In May 2004, the Acting Director for the Center for Drug Evaluation and Research (CDER) issued a "not-approvable" letter for the switch application, citing safety concerns about the use of Plan B in women under 16 years of age without the supervision of a health care practitioner. Because the not-approvable decision for the Plan B OTC switch application was contrary to the recommendations of FDA's joint advisory committee and FDA review staff, questions were raised about FDA's process for arriving at this decision. GAO was asked to examine (1) how the decision was made to not approve the switch of Plan B from prescription to OTC, (2) how the Plan B decision compares to the decisions for other proposed prescription-to-OTC switches from 1994 through 2004, and (3) whether there are age-related marketing restrictions for prescription Plan B and other prescription and OTC contraceptives. To conduct this review, GAO examined FDA's actions prior to the May 6, 2004, not-approvable letter for the initial application.

www.gao.gov/cgi-bin/getrpt?GAO-06-109.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7119 or crossem@gao.gov.

What GAO Found

On May 6, 2004, the Acting Director of CDER rejected the recommendations of FDA's joint advisory committee and FDA review officials by signing the not-approvable letter for the Plan B switch application. While FDA followed its general procedures for considering the application, four aspects of FDA's review process were unusual. First, the directors of the offices that reviewed the application, who would normally have been responsible for signing the Plan B action letter, disagreed with the decision and did not sign the not-approvable letter for Plan B. The Director of the Office of New Drugs also disagreed and did not sign the letter. Second, FDA's high-level management was more involved in the review of Plan B than in those of other OTC switch applications. Third, there are conflicting accounts of whether the decision to not approve the application was made before the reviews were completed. Fourth, the rationale for the Acting Director's decision was novel and did not follow FDA's traditional practices. The Acting Director stated that he was concerned about the potential behavioral implications for younger adolescents of marketing Plan B OTC because of their level of cognitive development and that it was invalid to extrapolate data from older to younger adolescents. FDA review officials noted that the agency has not considered behavioral implications due to differences in cognitive development in prior OTC switch decisions and that the agency previously has considered it scientifically appropriate to extrapolate data from older to younger adolescents.

The Plan B decision was not typical of the other 67 proposed prescription-to-OTC switch decisions made by FDA from 1994 through 2004. The Plan B OTC switch application was the only one during this period that was not approved after the advisory committees recommended approval. The Plan B action letter was the only one signed by someone other than the officials who would normally sign the letter. Further, there are no age-related marketing restrictions for any prescription or OTC contraceptives that FDA has approved, and FDA has not required pediatric studies for them. FDA identified no issues that would require age-related restrictions in the review of the original prescription Plan B new drug application.

In its comments on a draft of this report, FDA disagreed with GAO's finding that high-level management was more involved with the Plan B OTC switch application than usual, with GAO's discussion about when the not-approvable decision was made, and with GAO's finding that the Acting Director of CDER's rationale for denying the application was novel. However, GAO found that high-level management's involvement for the Plan B decision was unusual for an OTC switch application and FDA officials gave GAO conflicting accounts about when they believed the decision was made. The Acting Director acknowledged to GAO that considering adolescents' cognitive development as a rationale for a not-approvable decision was unprecedented for an OTC application, and other FDA officials told GAO that the rationale differed from FDA's traditional practices.

Contents

Letter 1

Results in Brief 5
Background 7
Aspects of FDA's Review of the Plan B Switch Application Were Unusual 13
Plan B Decision Was Not Typical of Other Proposed Prescription-to-OTC Switch Decisions 29
There Are No Age-Related Restrictions for Safety Reasons for Any FDA-Approved Contraceptives 30
Agency Comments and Our Evaluation 31

Appendix I **Scope and Methodology** 36

Appendix II **Not-Approvable Letter for the Prescription-to-OTC Switch Application of Plan B, May 6, 2004** 38

Appendix III **Timeline of Major Plan B Events Related to the Initial OTC Switch Application** 42

Appendix IV **Acting Director of CDER's Official Memorandum Explaining His Not-Approvable Decision, May 6, 2004** 47

Appendix V **Director of the Office of New Drugs' Official Memorandum on His Decision on the Plan B Application, April 22, 2004** 50

Appendix VI **Comments from the Food and Drug Administration** 53

Appendix VII **GAO Contact and Staff Acknowledgments** 57

Table

Table 1: Brief Timeline of Major Plan B Events Related to the Initial OTC Switch Application 15

Figure

Figure 1: Flow of an OTC Switch Application through the Decision Process within CDER for First-in-a-Class Drug 9

Abbreviations

ACRHD	Advisory Committee for Reproductive Health Drugs
CDER	Center for Drug Evaluation and Research
ECP	emergency contraceptive pill
FDA	Food and Drug Administration
NDA	new drug application
NDAC	Nonprescription Drugs Advisory Committee
OTC	over-the-counter
PDUFA	Prescription Drug User Fee Act
PREA	Pediatric Research Equity Act
sNDA	supplemental new drug application
STD	sexually transmitted disease
WCC	Women's Capital Corporation

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GAO
Accountability * Integrity * Reliability

United States Government Accountability Office
Washington, DC 20548

November 14, 2005

Congressional Requesters

In April 2003, Women's Capital Corporation (WCC) submitted an application to the Food and Drug Administration (FDA) requesting that the marketing status of its emergency contraceptive pill (ECP), Plan B, be switched from prescription to over-the-counter (OTC).[1] ECPs can be used to prevent unintended pregnancy when contraception fails or after unprotected intercourse, including cases of sexual assault. Plan B had been approved for use as a prescription drug by FDA in 1999 and is most effective when taken as soon as possible, but no later than 72 hours, after intercourse. By law, FDA may approve the switch of a prescription drug to OTC status if use of the drug is safe and effective for self-medication in accordance with proposed labeling.[2] Since 1975, when FDA formalized the current process for approving prescription-to-OTC switches, FDA has approved approximately 90 applications to change the marketing status of a prescription drug to OTC.

According to FDA's operational policies, reviews of OTC switch applications occur in its Center for Drug Evaluation and Research (CDER).[3] OTC switch applications for drugs that are "first-in-a-class,"[4] such as Plan B, are reviewed by two of the six offices of drug evaluation within CDER—including the Office of Drug Evaluation V, which reviews all OTC switch applications, and the office of drug evaluation that has the relevant expertise for the proposed switch drug.[5] In addition, CDER can request a joint meeting of advisory committees that it has established to seek scientific advice about its decisions from outside experts. The joint advisory committee meeting is conducted by the advisory committee that has expertise in OTC drugs and the advisory committee that has relevant expertise for the proposed OTC switch drug. After review of the OTC switch application and advice of the joint advisory committee, the directors of both offices of drug evaluation make a decision. If the directors of the offices concur on the decision for the application, they generally will both sign and issue an action letter.[6] If the directors do not concur with one another, the application is sent to the next level of review, the Director of the Office of New Drugs within CDER, who then makes the decision and signs and issues the action letter. However, the Director of CDER can also decide on an application and sign and issue the action letter.

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[1] FDA defines prescription-to-OTC switch as the OTC marketing of a product that was once a prescription drug product for the same indication, strength, dose, duration of use, dosage form, population, and route of administration. In this report, the phrase "OTC switch" refers to a prescription-to-OTC switch.

[2] See 21 U.S.C. § 353(b)(1); 21 C.F.R. § 310.200(b) (2005).

[3] FDA's operational policies are in its manuals of policies and procedures.

[4] A class of drugs refers to a category based on the chemical ingredients of the drugs. "First-in-a-class" refers to the first drug to be reviewed for an OTC switch within a class of drugs.

[5] In this report, FDA review staff refers to the staff in the Offices of Drug Evaluation III and V who reviewed the Plan B OTC switch application. The CDER structure described in this report is the one that existed at that time.

The Plan B application went to the Office of Drug Evaluation V, which includes the Division of Over-the-Counter Drug Products, and the Office of Drug Evaluation III, which includes the Division of Reproductive and Urologic Drug Products, where it was reviewed. In December 2003, a joint meeting of two FDA advisory committees, the Nonprescription Drugs Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD), recommended in a vote of 23 to 4 that the proposed OTC switch for Plan B be approved. FDA review staff also agreed that Plan B should be granted OTC status. On May 6, 2004, the Acting Director of CDER[7] signed a "not-approvable" letter for the switch to

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[6] An action letter is a written communication to the sponsor from FDA stating the outcome of the review of an application. The sponsor or applicant is the person or entity that assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations.

[7] The current Director of CDER was appointed to this position on July 29, 2005. However, he held the title of Acting Director from fall 2003 until his appointment. Prior to his appointment to Acting Director, he was Deputy Director of CDER. Because he was Acting Director during most of the time covered by this report—for those events associated with the initial Plan B OTC switch application through the May 6, 2004, decision—we use the title of Acting Director for him in this report.

OTC,[8] citing safety concerns about the use of Plan B in women under 16 years of age without the supervision of a practitioner licensed by law to administer the drug.[9] On July 22, 2004, Barr Pharmaceuticals, Inc.,[10] submitted an amended application for the proposed Plan B switch to market Plan B OTC for women 16 years of age and older and as a prescription drug for those under 16 years of age.[11]

Because the not-approvable decision for the initial Plan B OTC switch application was contrary to the recommendations of the joint advisory committee and the FDA review staff, you raised questions about FDA's process for arriving at its decision on the initial application. In this report, for the initial Plan B OTC switch application, we examined (1) how the decision was made to not approve the switch of Plan B from prescription to OTC, (2) how the Plan B decision compares to the decisions for other proposed prescription-to-OTC switches from 1994 through 2004, and (3) whether there are age-related marketing restrictions for prescription Plan B and other prescription and OTC contraceptives.

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[8] A not-approvable letter is a letter to the sponsor from FDA stating that the agency does not consider the application approvable because of one or more deficiencies in the application. See 21 C.F.R. § 314.120. There are two other types of action letters: the approval letter and the approvable letter. The approval letter indicates that the application is approved and the drug may go OTC. An approvable letter is similar to the not-approvable letter in that there are one or more deficiencies in the application precluding its approval. See 21 C.F.R. § 314.110. FDA officials stated that the difference between a not-approvable letter and an approvable letter is that a not-approvable letter is generally issued when more studies are required and an approvable letter is generally issued if there are sufficient data, but some outstanding concerns still exist.

[9] Besides physicians, other health care providers, such as nurse practitioners and physicians' assistants, may be licensed by law to administer drugs. While only FDA may change a drug's status from prescription to OTC, the practice of pharmacy is state controlled, allowing each state to decide who may prescribe a drug. While most states do not allow pharmacists to prescribe drugs, eight states (Alaska, California, Hawaii, Maine, Massachusetts, New Hampshire, New Mexico, and Washington) allow pharmacists to prescribe ECPs or provide them in accordance with approved physician protocols.

[10] In February 2004, WCC sold the rights to market Plan B to Barr Pharmaceuticals, Inc. In October 2003, as the purchase of Plan B by Barr Pharmaceuticals, Inc., was being finalized, Barr began acting as the agent for WCC regarding Plan B.

[11] On August 26, 2005, FDA announced it had completed its review of the amended application and concluded that the scientific data were sufficient to support the safe use of Plan B in an OTC setting for women 17 years of age and older. However, FDA delayed taking action on the amended application to seek public comment on marketing issues related to this decision. See also Drug Approvals: Circumstances Under Which an Active Ingredient May Be Simultaneously Marketed in Both a Prescription Drug Product and an Over-the-Counter Drug Product, 70 Fed. Reg. 52050 (2005). Accordingly, as of November 4, 2005, Plan B may not be legally marketed OTC.

To address our objectives, we examined documents, including the official minutes from meetings of FDA staff and the written reviews of the adequacy of the Plan B OTC switch application prepared by FDA staff in the Offices of Drug Evaluation III and V and the Office of New Drugs, related to the review of, and decision on, the Plan B OTC switch application, and we interviewed FDA staff and officials who conducted the reviews and were involved in the decision. We also reviewed FDA's manuals of policies and procedures and *The CDER Handbook* to determine how FDA considers an application to switch a drug from prescription to OTC.[12] We interviewed members of FDA's two advisory committees that met jointly to discuss the Plan B OTC switch application, and we reviewed the transcript of its meeting. We compared the FDA decision for Plan B to FDA's decisions for other proposed prescription-to-OTC switch applications from 1994 through 2004. We interviewed officials from Barr Pharmaceuticals, Inc., the company currently sponsoring the Plan B application for the prescription-to-OTC switch, and WCC, the original sponsor of the Plan B switch application. In addition, we reviewed documents and interviewed FDA officials regarding age-related marketing restrictions for prescription Plan B and other prescription and OTC contraceptives. We also interviewed representatives from the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, Concerned Women for America, and the Planned Parenthood Federation of America, Inc., regarding FDA's safety concerns for Plan B and other contraceptives. Our work examined only events and communications within FDA and between FDA and the Plan B sponsor; we did not consider any communications that may have occurred between FDA officials and other executive agencies. Our work examined only FDA's actions prior to the May 6, 2004, not-approvable letter for the initial application, and we did not examine aspects of FDA's subsequent deliberations about Plan B. (See app. I for details regarding our scope and methodology and app. II for a copy of the May 6, 2004, not-approvable letter for the initial application.) We conducted our work from September 2004 through November 2005 in accordance with generally accepted government auditing standards.

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[12] *The CDER Handbook* contains information on the center's processes and activities. It was created for industry officials, health professionals, academics, and the general public, and it is available at www.fda.gov/cder/handbook/startpag.htm (downloaded Dec. 8, 2004).

Results in Brief

On May 6, 2004, the Acting Director of CDER rejected the recommendations of the joint advisory committee and FDA review officials by signing the not-approvable letter for the Plan B switch application, concluding a review process that began on April 16, 2003, when WCC submitted a standard supplemental new drug application (sNDA) requesting that Plan B be made available without a prescription. While FDA followed its general procedures for considering the application, four aspects of FDA's review process were unusual. First, the Directors of the Offices of Drug Evaluation III and V, who would normally have been responsible for signing the Plan B action letter, disagreed with the decision and did not sign the not-approvable letter for Plan B. The Director of the Office of New Drugs also disagreed and did not sign the letter. Second, FDA's high-level management was more involved in the review of Plan B than in those of other OTC switch applications. For example, FDA review staff told us that they were told early in the review process that the decision would be made by high-level management. Third, as documented in the reviews of FDA staff and in our interviews with FDA officials, there are conflicting accounts of whether the decision to not approve the application was made before the reviews were completed. Fourth, the rationale for the Acting Director of CDER's decision was novel and did not follow FDA's traditional practices. Specifically, the Acting Director was concerned about the potential impact that the OTC marketing of Plan B would have on the propensity for younger adolescents to engage in unsafe sexual behaviors because of their lack of cognitive maturity compared to older adolescents. He also stated that it was invalid to extrapolate data from older to younger adolescents in this case. FDA review officials noted that the agency has not considered behavioral implications due to differences in cognitive development in prior OTC switch decisions and that the agency has considered it scientifically appropriate to extrapolate data from older to younger adolescents.

The decision to not approve the Plan B OTC switch application was not typical of the other 67 prescription-to-OTC switch decisions made from 1994 through 2004. FDA's joint advisory committee considered 23 OTC switch applications during this period; the Plan B OTC switch application was the only 1 of those 23 that was not approved after the joint committee voted to recommend approval of the application. Also, the Plan B action letter was the only one signed by the Director of CDER, in this case the Acting Director of CDER, instead of the directors of the offices or divisions that reviewed the application, who would normally sign an action letter.

There are no age-related marketing restrictions for safety reasons for any of the prescription or OTC contraceptives that FDA has approved, and FDA has not required pediatric studies for them. All FDA-approved OTC contraceptives are available to anyone, and all FDA-approved prescription contraceptives are available to anyone with a prescription. For hormonal contraceptives, FDA assumes that suppression of ovulation would be the same for any female after menarche,[13] regardless of age. FDA did not identify any issues that would require age-related restrictions in its review of the original application for prescription Plan B, and prescription Plan B is available to women of any age.

In its comments on a draft of this report, FDA disagreed with three of our findings. First, FDA disagreed with our finding that the involvement of high-level management in the Plan B decision was unusual because their involvement is likely in high-profile and controversial regulatory decisions. Although we agree that high-level management involvement is more likely to occur with high-profile regulatory decisions, we found that the level of high-level management involvement for the Plan B decision was unusual for OTC switch applications. The other examples of high-level management involvement given to us by FDA officials during the course of our work involved decisions about the marketing of prescription drugs. Second, FDA disagreed with our discussion about when the decision to deny the switch application was made. We maintain that the draft report accurately noted that FDA officials gave us conflicting accounts about when they believed the not-approvable decision was made. Third, FDA disagreed with our finding that the Acting Director of CDER's rationale for denying the application was novel and did not follow FDA's traditional practices. We found that the Acting Director's rationale was novel because it explicitly considered the differing levels of cognitive maturity of adolescents of different ages, and that, because of the Acting Director's views about these differences in cognitive maturity, he concluded that it was inappropriate to extrapolate data related to risky sexual behavior from older to younger adolescents. The Acting Director acknowledged to us that considering adolescents' cognitive development as a rationale for a not-approvable decision was unprecedented for an OTC application. In addition, other FDA officials told us that the agency had not previously considered whether younger adolescents would use a product differently than older adolescents. Therefore, we believe that our finding is correct and we have revised the report to more clearly describe the reasons for our finding.

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[13] Menarche is the initial menstrual period, normally occurring between a female's 9th and 17th year.

Background

Within FDA, CDER oversees the switch of drugs from prescription to OTC. Generally, prescription drugs are drugs that are safe for use only under the supervision of a health care practitioner. Approved prescription drugs that no longer require such supervision may be marketed OTC.[14] In applying this standard, FDA will authorize a prescription-to-OTC switch only after it is determined that the drug in question has met the following FDA criteria: (1) it has an acceptable safety profile based on prescription use and experience;[15] (2) it has a low potential to be abused; (3) it has an appropriate safety and therapeutic index;[16] (4) it has a positive benefit–risk assessment; and (5) it is needed for a condition or illness that is self-recognizable, self-limiting,[17] and requires minimal intervention by a health care practitioner for treatment.[18] FDA tries to determine if the OTC availability of a prescription drug will prevent or delay someone from seeking needed medical attention.

One class of OTC drugs switched from prescription status, the nicotine products (such as Nicorette gum), has restricted access based on age—they are available OTC only to persons 18 years of age or older.

Studies for Prescription-to-OTC Switches

Generally, drugs considered for a prescription-to-OTC switch involving the same indication, strength, dose, duration of use, dosage form, patient population, and route of administration as the prescription drug require fewer new studies regarding safety and efficacy because such studies have already been submitted as part of the original new drug application

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[14] See 21 U.S.C. § 353(b)(1), 21 C.F.R. § 310.200(b).

[15] An appropriate safety profile means that a drug that has been on the market has proven that it continues to be safe.

[16] The safety and therapeutic index is the ratio between the toxic dose and the therapeutic dose of a drug and is used as a measure of the relative safety of the drug for a particular treatment.

[17] A self-limiting condition or illness is one that without treatment runs a definite course within a limited period.

[18] These criteria are from the transcript of the joint advisory committee meeting held on December 16, 2003, to discuss the Plan B OTC switch application. They were presented by an FDA official at the meeting.

(NDA).[19] FDA also requires sponsors to address concerns related to consumers' ability to self-diagnose and self-treat the condition. Thus, sponsors generally submit additional studies, such as an actual use study, which examines consumers' ability to self-diagnose, and a label comprehension study, which examines how consumers interpret the drug's proposed label. In addition to these actual use and label comprehension studies, FDA requires sponsors to submit updated safety information on adverse events reported for the prescription form of the drug.

FDA Process for Switching First-in-a-Class Prescription Drug to OTC

Figure 1 shows the flow of an OTC switch application of a first-in-a-class drug through the decision process within CDER. To begin the process for a prescription-to-OTC switch, the sponsor submits an efficacy supplement to an approved NDA.[20] This sNDA is sent to the FDA Office of Drug Evaluation that oversaw the original NDA and usually is the office with relevant expertise. This Office of Drug Evaluation is generally responsible for reviews of the primary effectiveness data and safety results. After an application has been determined to be complete, a reviewer from this office assesses the design, general effectiveness, and safety of the product. If the application is determined to be incomplete, this office will issue a "refusal to file" letter to the sponsor, detailing the omissions or inadequacies that led to this decision.

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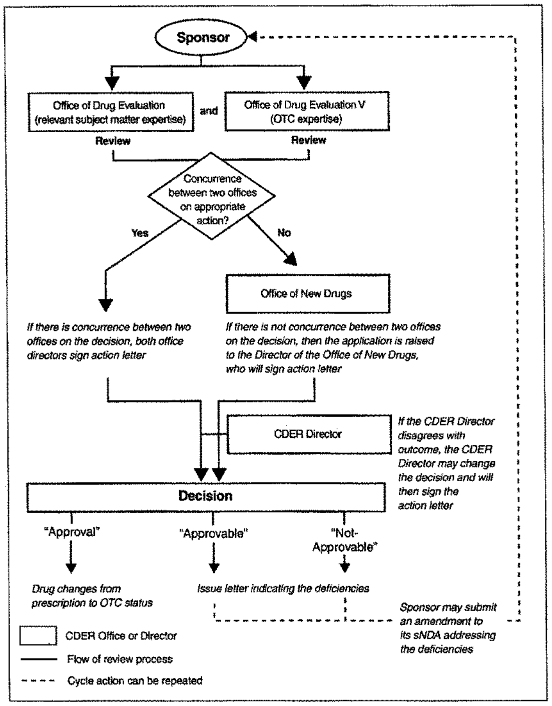
[19] Drugs that involve a different indication, strength, dose, duration of use, dosage form, patient population, or route of administration may require additional efficacy and safety studies. For example, the OTC switch of ibuprofen in 1984 was for a lower dose than prescription ibuprofen and, therefore, required new studies showing the efficacy of the lower dose.

[20] An efficacy supplement may include a submission for proposed changes in the labeling of an approved product for a new indication, new dosage regimen, or significant alteration in the patient population.

Figure 1: Flow of an OTC Switch Application through the Decision Process within CDER for First-in-a-Class Drug


Sponsor
Office of Drug Evaluation (relevant subject matter expertise)
and
Office of Drug Evaluation V (OTC expertise)
Review
Review
Concurrence between two offices on appropriate action?
Yes
No
Office of New Drugs
If there is concurrence between two offices on the decision, both office directors sign action letter
If there is not concurrence between two offices on the decision, then the application is raised to the Director of the Office of New Drugs, who will sign action letter
CDER Director
If the CDER Director disagrees with outcome, the CDER Director may change the decision and will then sign the action letter
Decision
"Approval"
"Approvable"
"Not-Approvable"
Drug changes from prescription to OTC status
Issue letter indicating the deficiencies
Sponsor may submit an amendment to its sNDA addressing the deficiencies
CDER Office or Director
Flow of review process
Cycle action can be repeated

Source: FDA.

Note: As part of their decision process, the Offices of Drug Evaluation also get input from CDER's Office of Drug Safety. They also may convene a meeting of advisory committees.

When an Office of Drug Evaluation with relevant expertise receives a fileable sNDA for an OTC drug switch, it notifies the Office of Drug Evaluation V and its Division of Over-the-Counter Drug Products, which has relevant expertise in OTC drug products. Generally, the Office of Drug Evaluation V oversees the review of (1) the suitability of the product for OTC use and (2) safety experiences during the marketing of the prescription product. A reviewer from this office assesses studies related to OTC marketing, including the actual use and label comprehension studies. CDER's Office of Drug Safety conducts additional reviews of the label comprehension studies, reviews postmarketing safety data of the prescription drug, and provides reports to reviewing staff in other offices upon request.

FDA can convene advisory committee meetings for prescription-to-OTC switch applications. Advisory committees include outside experts, such as medical professionals and researchers, who provide FDA with independent advice and recommendations. Members review data submitted by the sponsor or presented by FDA review staff, address questions, and vote, either supporting or opposing a switch from prescription-to-OTC status. Advisory committees conduct open meetings and offer members of the public the opportunity to express their views. FDA considers the advisory committees' recommendations in its deliberations. However, the agency decides whether to adopt these recommendations on a case-by-case basis and is not required to follow the committees' recommendations.

FDA review staff from the appropriate offices of drug evaluation review the data presented, interpret the findings, and make recommendations to the respective office directors on whether the proposed OTC switch should be approved. Once these reviews are completed, they are sent to the directors of both the office of drug evaluation with relevant expertise and the Office of Drug Evaluation V. If both directors agree with each others' review recommendation, the directors of the relevant offices of drug evaluation prepare an action package[21] and an appropriate action letter for review, concurrence, and their final signatures. If the office directors do not concur on the decision, the application is reviewed by the Office of New Drugs. The Director of CDER is not directly involved in the approval of all drugs, but may overrule the decisions of subordinate officials.

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[21] An action package is a compilation of (1) FDA-generated documents related to the review from submission to final action of an NDA or efficacy supplement from the sponsor; (2) documents, such as meeting minutes and pharmacology reviews, pertaining to the format and content of the application; and (3) labeling submitted by the sponsor.

The authority to approve an OTC switch application ultimately rests with the Secretary of Health and Human Services. This approval authority is delegated to the Commissioner of FDA, then to other high-level management officials, and eventually to other FDA officials within lower levels of the agency. This delegated authority allows decisions to be made at lower levels within the agency but assumes that management agrees with these decisions. The FDA Commissioner and other officials within the Office of the Commissioner usually do not have a role in OTC switch decisions, but have the authority to overrule the decisions of other FDA officials.

Contraceptives

There are several types of contraceptive drugs and devices, including barrier methods, intrauterine devices, spermicides, and hormonal methods. Several types of hormonal methods of contraception are available, including birth control pills, injectable hormones, hormonal implants, and ECPs. FDA has approved two ECPs, Preven and Plan B, for use by prescription, and Plan B is the first drug in its class to go through the review process by FDA to determine whether it should be allowed to be sold OTC.[22] ECPs are high dose birth control pills and have been available by prescription since 1998, when FDA approved Preven, a dedicated[23] combined ECP containing the hormones estrogen and progestin.[24] Prior to 1998, many physicians instructed patients to take higher doses of oral contraceptive pills for emergency contraception, an "off-label" use.[25]

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[22] In 1997, a notice in the *Federal Register* stated that the Commissioner of FDA had concluded that certain combined oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as emergency contraception, and requested submission of NDAs for this use. See Prescription Drug Products; Certain Combined Oral Contraceptives for Use as Postcoital Emergency Contraception, 62 Fed. Reg. 8610 (1997). In 2004, the manufacturer stopped production of Preven.

[23] A dedicated ECP is a drug expressly meant for use as an ECP; levonorgestrel is a synthetic progestin commonly used in birth control pills.

[24] Estrogen is a hormone that is responsible for cyclic changes in the vagina and uterus. Progestin is a hormone that prepares the endometrium for implantation of the fertilized egg. These hormones in oral birth control pills suppress ovulation.

Emergency Contraceptive Plan B

Plan B is a dedicated ECP containing only levonorgestrel, a type of progestin. The Plan B regimen is a two-pill dose of levonorgestrel (0.75 mg each) that is most effective when the first pill is taken as soon as possible, but no later than 72 hours, after contraceptive failure or unprotected intercourse. The second pill is taken 12 hours after the first pill. Research suggests that a levonorgestrel-only hormone regimen, such as Plan B, can reduce the risk of pregnancy by 89 percent if taken within the 72-hour window.[26] The time constraint for maximum effectiveness associated with Plan B has led many in the medical community and some reproductive health advocates to support switching Plan B to OTC, making it more readily available when needed. In addition, levonorgestrel-only regimens, such as Plan B, have fewer side effects than the combined ECP, reducing the incidence of two common side effects, nausea and vomiting, by 50 percent and 70 percent, respectively.

Research has shown that levonorgestrel-only hormonal emergency contraception, such as Plan B,[27] interferes with prefertilization events. It reduces the number of sperm cells in the uterine cavity, immobilizes sperm, and impedes further passage of sperm cells into the uterine cavity. In addition, levonorgestrel has the capacity to delay or prevent ovulation from occurring.[28]

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[25] Off-label drug use occurs when physicians prescribe a drug for clinical indications other than those listed on the label.

[26] World Health Organization, "Randomized Controlled Trial of Levonorgestrel Versus the Yuzpe Regimen of Combined Oral Contraceptives for Emergency Contraception," *The Lancet*, vol. 352 (1998): 428-433.

[27] Horacio B. Croxatto and others, "Mechanism of Action of Hormonal Preparations Used for Emergency Contraception: A Review of the Literature," *Contraception*, vol. 63 (2001): 111-121; and H.B. Croxatto and others, "Pituitary-Ovarian Function Following the Standard Levonorgestrel Emergency Contraceptive Dose or a Single 0.75-mg Dose Given on the Days Preceding Ovulation," *Contraception*, vol. 70 (2004): 442-450.

[28] Ovulation occurs when a mature egg is released from the ovary, is pushed down the fallopian tube, and is available to be fertilized.

product." In addition, according to meeting minutes, the Commissioner requested a "rapid action" on the Plan B OTC switch application.[40]

Four Aspects of FDA's Review of the Plan B OTC Switch Application Were Unusual

Aspects of FDA's review of the Plan B OTC switch application were unusual compared to the agency's regular review process. First, the FDA officials who would normally sign an action letter for an OTC switch application disagreed with the decision and did not sign the Plan B not-approvable letter; as a result, the Acting Director of CDER did so. Second, the review process for the Plan B OTC switch application was marked by a level of involvement by FDA high-level management that has not been typical for OTC switch applications. Third, conflicting accounts exist regarding when the decision to deny the application was made. Finally, the Acting Director of CDER's rationale for denying the application was novel for an OTC switch decision.

FDA Officials Normally Responsible for Signing the Action Letter Did Not Do So

By early April 2004, the reviews from the Offices of Drug Evaluation III and V were completed. The directors of these offices agreed with the recommendations of the joint advisory committee and review staff that Plan B should be made available without a prescription. Nonetheless, the office directors told us that they were asked by high-level management to draft a not-approvable letter. Both office directors also told us they did not agree with a not-approvable action and did not sign the not-approvable letter.

The issue was then raised to the Office of New Drugs. The Director of the Office of New Drugs reviewed the staff's analysis of the application and concurred with the recommendations of both office directors. He also did not sign the not-approvable letter. The Director of the Office of New Drugs told us that it was "very, very rare" that his office would become involved in the signing of an action letter. According to FDA manuals of policies and procedures and *The CDER Handbook*, the Office of New Drugs would review decisions from the offices of drug evaluation only if there was disagreement between these two reviewing offices. In the case of Plan B, there was no disagreement between the two reviewing offices of drug evaluation on the approvability of the application.

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[40] We attempted to interview the individual who had been the Commissioner of FDA until March 2004. We were unable to arrange an interview, and he did not respond to written questions we submitted. However, he did provide a written comment to us. The former Commissioner noted that the initial Plan B decision was made after he left FDA and that his interactions with the Acting Director of CDER and other FDA staff in this case were consistent with his usual practices. We also attempted to interview the individual who had been the Deputy Commissioner until March 2004, when he became the Acting Commissioner (we refer to him as Deputy Commissioner in this report). We were unable to arrange an interview with him or obtain a response to our written questions prior to his departure from FDA in September 2005. His attorney subsequently provided a written statement on his behalf. According to the statement: (1) the Deputy Commissioner did not have a role in the review of the Plan B switch application; (2) the Acting Director of CDER briefed him after he became Acting Commissioner on the Acting Director's conclusions regarding Plan B, and he concurred with the Acting Director's decision; and (3) the Deputy Commissioner did not read the reviews of the application by the staff from the Offices of Drug Evaluation III and V and by the Director of the Office of New Drugs, and therefore, could not have any comments or concerns.

The Acting Director of CDER signed the not-approvable letter, which was issued on May 6, 2004. According to FDA, the Acting Director of CDER did not ask the Directors of the Offices of Drug Evaluation III and V or the Director of the Office of New Drugs to sign the not-approvable letter, nor was the letter presented to them for their signature, because it was known that they did not agree with the not-approvable action.

High-Level FDA Management Was More Involved Than Usual in the Review Process for the Plan B Prescription-to-OTC Switch Application

High-level FDA management became more involved than usual in the review process for the Plan B OTC switch application. According to review staff within the Offices of Drug Evaluation III and V that we spoke with and as documented in their respective reviews, at a meeting held on January 15, 2004, the Acting Director of CDER informed them that the decision for the Plan B OTC switch application would be made by high-level management. This action removed decision-making authority from the directors of the reviewing offices who would normally make the decision. According to minutes from a subsequent meeting between review officials and the sponsor on January 23, 2004, the Director of the Office of New Drugs informed the sponsor that such a high-level decision was not typical of CDER's procedures for drug approvals.

The Acting Director of CDER told us that management needed to be comfortable with review staff's final decision because of the high visibility and sensitivity of the Plan B OTC switch application. He and other senior FDA officials told us that involvement by high-level management stemmed from the agency's practice of delegated authority. In addition to highly visible and sensitive cases, they said that the Commissioner and the Director of CDER would also generally become involved in cases that would potentially have a far-reaching impact or in cases in which management had a different view or disagreed with review staff. Although such cases are rare, FDA officials cited other examples when high-level management was more involved in the review process for a drug application than normal—the approval of thalidomide for the treatment of leprosy in 1998[41] and the approval of mifepristone for the termination of early pregnancy in 2000.[42] Unlike Plan B, the examples FDA officials provided us did not involve OTC switch applications.

FDA Officials Gave Conflicting Accounts of When the Decision to Not Approve Plan B Was Made

FDA officials gave conflicting accounts of when the not-approvable decision for the Plan B OTC switch application was made. FDA officials, including the Director and Deputy Director of the Office of New Drugs and the Directors of the Offices of Drug Evaluation III and V, told us that they were told by high-level management that the Plan B OTC switch application would be denied months before staff had completed their reviews of the application. The Director and Deputy Director of the Office of New Drugs told us that they were told by the Acting Deputy Commissioner for Operations[43] and the Acting Director of CDER, after the Plan B public meeting in December 2003, that the decision on the Plan B application would be not-approvable. They informed us that they were also told that the direction for this decision came from the Office of the Commissioner. The Acting Deputy Commissioner for Operations and the Acting Director of CDER denied that they had said that the application would not be approved. In addition, although minutes of the January 15, 2004, meeting stated that the Acting Director told review staff that a not-approvable decision was "recommended," review staff documented that they were told at this meeting that the decision would be not-approvable. Both office reviews were not completed until April 2004.

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[41] Leprosy is a chronic bacterial infection that primarily affects the skin, nerves, and mucus membranes and causes deformities of the face and extremities. For the thalidomide NDA, the Director of CDER at that time disagreed with review staff on whether the NDA should be approved. Review staff were concerned about the potential off-label use of the drug. However, the Director disagreed and overruled review staff and approved the thalidomide NDA.

[42] For mifepristone, there was no disagreement between high-level management and the review staff on whether the NDA should be approved. Rather, the Commissioner at that time signed the approval letter out of concern regarding the protection of the identities of staff that had reviewed the application.

[43] The Acting Deputy Commissioner for Operations was the Director of CDER when the initial Plan B OTC switch application was submitted in April 2003. She told us that she became the Acting Deputy Commissioner for Operations in March 2004, and that her role in the review of the initial Plan B OTC switch application was as a consultant to the Acting Director of CDER.

However, the Acting Director of CDER told us that he made the decision to not approve the Plan B OTC switch application shortly before signing the action letter. He also informed us that his decision was made in consultation with other high-level management officials, including the Commissioner and the Acting Deputy Commissioner for Operations, but that he was not directed to reach a particular decision. The Acting Director also told us that these high-level management officials agreed with his decision. When we asked the Acting Director about his meeting with officials from the Office of New Drugs in December 2003, he told us that he might have indicated to the Director and Deputy Director that the agency was "tending" or "thinking of going" in the direction of a not-approvable decision, but that this was not the final decision. Furthermore, although he told us that he was "90 percent sure" as early as January 2004, that the decision would be not-approvable, the Acting Director told us he made his final decision only in the last few weeks prior to issuing the action letter, after he had reviewed all of the documentation associated with the application.

The Acting Director of CDER told us that the rationale for his decision was not fully developed until a few days before the action letter was issued on May 6, 2004. According to internal FDA e-mails we reviewed, the Acting Director of CDER contacted the Director of the Office of Pediatric Therapeutics on May 2, 2004, requesting assistance on language regarding cognitive development during early adolescence to support his decision. According to these e-mails, the Director of the Office of Pediatric Therapeutics responded that she would consult with another official with a background in developmental pediatrics and would follow up with "behavioral science information as to why one cannot extrapolate decision making on safety issues" from older to younger adolescents.

The Acting Director's Rationale for the Not-Approvable Decision Was Novel and Varied from FDA's Traditional Practices

The rationale for the Acting Director of CDER's decision was novel and did not follow FDA's traditional practices. The Acting Director was concerned about the potential impact that the OTC marketing of Plan B would have on the propensity for younger adolescents to engage in unsafe sexual behaviors because of their lack of cognitive maturity. The Acting Director further concluded that because these differences in cognitive development made it inappropriate to extrapolate data from older to younger adolescents in this case, there was insufficient data on the use of Plan B among younger adolescents. FDA review officials disagreed with the Acting Director's rationale and noted that the agency had not considered behavioral implications resulting from differences in cognitive development in prior OTC switch decisions.

The Acting Director's Rationale Was Based on His Concerns about Risk-Taking in Younger Adolescents

The Acting Director of CDER told us he signed the not-approvable letter because of his concerns about the lack of cognitive development and the potential for risky behaviors among younger adolescents resulting from increased access to Plan B. For example, he noted increased access to Plan B could potentially result in an increase in unsafe sexual activity, particularly among younger adolescents—an age group, he noted, that has a tendency to engage in risky behaviors because of their level of cognitive development. This change in behavior could be represented by changes in measurable indicators, such as a decrease in condom use or an increase in the transmission of sexually transmitted diseases (STD).[44]

In his memorandum on his review of the Plan B OTC switch application, the Acting Director of CDER also stated that because younger adolescents' cognitive maturity related to controlling impulsive behavior is less developed than older adolescents', he did not consider it appropriate to extrapolate data from older to younger adolescents in this case. (See app. IV for a copy of the Acting Director of CDER's memorandum.) He specifically noted the following:

> "In making decisions about pediatric use, it is often possible to extrapolate data from one age group to another, based on knowledge of the similarity of the condition. However, in this case, adolescence is known to be a time of rapid and profound physical and emotional change. . . . Because of these large developmental differences, I believe that it is very difficult to extrapolate data on behavior from older ages to younger ages. I am uncomfortable with our current level of knowledge about the potential differential impact of OTC availability of Plan B on these age subsets."

Some other officials we spoke with supported the Acting Director's concerns about extrapolating data from older to younger adolescents. For example, the Director of the Office of Pediatric Therapeutics told us and noted in e-mails to the Acting Director of CDER, which we reviewed, that the difference in cognitive development and maturity between older and younger adolescents and the potential impact this would have on behaviors warranted a separate analysis of this latter age group. In addition, one of the members of the joint advisory committee we spoke with said he was also concerned about extrapolating data from older to younger age groups because he perceived weaknesses in the actual use and label comprehension studies submitted by the sponsor.[45]

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[44] For the actual use study for the Plan B OTC switch application, an additional observation was included along with the two study objectives. This observation involved collecting and comparing data from study participants on the use of emergency and regular contraception, such as a change in condom use. These data were collected at the time participants enrolled in the study and compared to data collected during a follow-up, 4 weeks later. However, although these data were considered relevant to the application by the sponsor and FDA officials, the sponsor noted that the actual use study was not primarily designed for assessing the potential risk behaviors of potential users of Plan B in an OTC setting.

Because of these concerns, the Acting Director concluded that the Plan B OTC switch application needed more data specific to younger adolescents. In the not-approvable letter, the Acting Director stated there were too few younger adolescents in the sponsor's actual use study to support the Plan B OTC switch application. Specifically, he highlighted that only 29 of 585 participants in the study were 14 years to 16 years of age and none were under 14 years of age. Although he acknowledged concerns about the difficulty of including younger adolescents in actual use studies, he told us that it was not impossible to enroll younger adolescents in studies, noting that studies for other products have been conducted involving younger participants, including those as young as infants. Some of the Acting Director's concerns regarding the low number of younger adolescents were also raised by other review staff and members of the joint advisory committee. For example, one FDA reviewer who recommended an approvable action on the Plan B OTC switch application noted that despite a reanalysis of the actual use study data of subjects aged 14 years to 17 years, the sample size was too small and "significantly limit[ed] assessment of potential risky/unsafe sexual behavior associated with OTC accessibility of Plan B."

Although review staff within the Offices of Drug Evaluation III and V presented him with additional data on sexual behaviors of younger adolescents in association with increased access to ECPs, the Acting Director of CDER determined that these data were not adequate to support the approval of Plan B for OTC use. He provided his reasoning in his memorandum, stating that these studies were either "not conducted in the general population or they provide[d] product education assistance beyond what adolescents would receive in an OTC situation, where no contact with a health care professional is expected."

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[45] This committee member told us he was specifically concerned that the actual use study was largely conducted in family planning clinics, saying this could bias the results of the study by potentially introducing study participants to health care professionals who could educate them on the use of ECPs. For the label comprehension study, he was concerned about the poor results among lower-educated participants. This committee member told us that literacy and age were a concern because younger age groups are by definition considered among the lower educated.

The Acting Director of CDER's rationale varied from FDA's traditional practices by considering the potential implications OTC access of Plan B would have on the sexual behavior of younger adolescents based on their lack of cognitive maturity and by not accepting the validity of extrapolating data from older to younger adolescents. Although he acknowledged to us that considering adolescents' cognitive development as a rationale for a not-approvable decision was unprecedented, the Acting Director also told us that FDA had recently increased its focus on pediatric issues. He noted that pediatric issues were currently being raised in prescription drug reviews and believed the same should occur in OTC drug reviews.

FDA Review Officials Disagreed with the Acting Director's Rationale for the Not-Approvable Decision

FDA review staff, the Directors of the Offices of Drug Evaluation III and V, and the Director of the Office of New Drugs disagreed with the Acting Director of CDER's rationale for not approving the Plan B OTC switch application. FDA review officials, including those from the Office of New Drugs, noted that traditionally FDA has not considered whether younger adolescents would use an OTC product differently than older adolescents, and the Director of the Office of New Drugs told us that it was "atypical" to raise the question of maturity during a drug review. These officials also noted that FDA does not attempt to determine how a patient arrived at the need for a drug. Rather, drug evaluations usually begin with the need for a potential treatment already existing.

Review staff we spoke with acknowledged that certain behavioral concerns and unintended consequences are examined for an OTC switch application, such as whether making a drug OTC would delay a person from seeking medical treatment or if the drug would potentially be abused if it were more readily available. They told us that these issues are usually examined during a benefit–risk review, which is an analysis of potential medical outcomes. Review staff told us they examined benefit–risk issues for Plan B, and they concluded that concerns regarding the potential for unsafe sexual behaviors among adolescents could not be supported.[46] In addition, the review of the label comprehension study from the Office of Drug Safety noted that potential users of the product would be able to appropriately use it if the sponsor made its suggested changes to the proposed labeling.[47] Also, at the public meeting, members of the joint advisory committee voted 27 to 1 that the actual use study demonstrated that consumers could properly use Plan B as recommended by the label. The members of the joint advisory committee also voted 28 to 0 that the literature review of Plan B included in the actual use study did not show that Plan B would be used as a regular form of contraception.

Furthermore, the review of the application from the Office of Drug Evaluation III, which included the benefit–risk assessment for Plan B, noted that having Plan B in an OTC setting would "pose little risk" to the potential user and that the risk of an adverse pregnancy outcome, such as lower birth weight babies and premature delivery, is much higher among younger adolescents. The review concluded that OTC access to Plan B in helping younger adolescents avoid unintended pregnancies would be "of particular value given the greater risk of an adverse pregnancy outcome in this high risk group." This review also noted that even for a large dose of the hormone used in Plan B, the "margin of safety appear[ed] to be high."

In an attempt to further address the Commissioner's and Acting Director's concerns about the potential for increased risky behavior by younger adolescents resulting from increased access to Plan B, review staff requested additional data from the sponsor and reviewed ongoing studies examining these concerns. FDA's reviewers concluded that increased access to ECPs did not result in (1) inappropriate use by adolescents as a substitute form of contraception, (2) an increase in the number of sexual partners or the frequency of unprotected intercourse, or (3) an increase in the frequency of STDs.

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[46] Only one of the review staff for the Plan B OTC switch application raised concerns regarding behaviors of younger adolescents. Recommending an approvable decision, he concluded in his written review of the application that (1) the actual use study had insufficient data on whether OTC accessibility of Plan B might be associated with risky (or unsafe) sexual behaviors over the long term, particularly among adolescents; (2) the behavioral literature did not provide strong evidence to address the inadequacies in the actual use study in assessing risky sexual behaviors in the target OTC populations; and (3) some behavioral studies in the literature suggested that providing ECPs in advance could encourage unsafe sexual behaviors in the study populations.

[47] The changes proposed by the Office of Drug Safety were included as attachments to the office's review of the label comprehension study.

To reach these conclusions, review staff examined the five studies that provided supplies of ECPs in advance to study participants to assess the behavioral impact of OTC access. In one study, which included 2,090 women aged 15 years to 24 years, there was a decrease in unprotected sex among all age groups and no increase in the incidence of STDs compared to the baseline. Another study of 160 adolescent mothers included participants aged 14 years to 20 years. Although there were limited data available, this study concluded that there was no increase in unprotected intercourse and no decrease in condom use among participants. A third study of 301 adolescent women, aged 15 years to 20 years, showed similar results, with no increase in unprotected intercourse or STDs and no decrease in condom use.

FDA officials, including those from the Office of New Drugs, also disagreed with the Acting Director's determination that extrapolating data from older populations to younger adolescents was inappropriate. In their reviews, officials noted that data they reviewed showed that younger adolescents had outcomes similar to those of older populations. For example, the actual use study found that 82 percent of participants 16 years of age or under correctly took the second dose 12 hours later, compared to 78 percent of those 17 years and older.[48] Also, review staff said that overall the number of participants who were younger adolescents was adequate to draw conclusions about potential use among the adolescent population. Review staff told us they encouraged the sponsor to not limit enrollment or exclude adolescents from the actual use study and felt the study included a representative population of women that would potentially use Plan B. Some of the members of the joint advisory committee we spoke with also said they considered the number of younger adolescents in the actual use study as adequate.

In addition, the Director of the Office of New Drugs told us that the agency has not requested age-specific data often and that FDA often extrapolates findings, including findings on behaviors, from adults to adolescents. He added that given the agency's traditional processes and the data provided in the Plan B OTC switch application, there was no reason to consider the extrapolations done in the staff's reviews as inappropriate.

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[48] Although there were 29 younger adolescents aged 16 years or under enrolled in the actual use study, only 22 used the product and provided follow-up data for this specific question. Of the 22 study participants who used the product and provided follow-up data, 18 reported that they correctly took the second dose 12 hours after the first. The total number of study participants aged 17 years or older who also used the product and provided follow-up data was 46. Of these 46 study participants, 36 reported that they correctly took the second dose 12 hours after the first.

Based on the reviews conducted by review staff and on the recommendations of the joint advisory committee, the Director of the Office of New Drugs concluded the following in his memorandum of his review of the Plan B OTC switch application, issued April 22, 2004 (a copy of this memorandum can be found in app. V):

> "In my opinion, these studies provide adequate evidence that women of childbearing potential can use Plan B safely, effectively, and appropriately for emergency contraception in the non-prescription setting. The data submitted by the sponsor in support of non-prescription use of Plan B are fully consistent with the Agency's usual standards for meeting the criteria for determining that a product is appropriate for such use. . . . Such a conclusion is consistent with how the Agency has made determinations for other OTC products, including other forms of contraception available without a prescription. Further, I believe that greater access to this drug will have a significant positive impact on the public health by reducing the number of unplanned pregnancies and the number of abortions."

In his memorandum, the Director of the Office of New Drugs also noted that FDA has a "long history" of extrapolating findings from older populations to younger adolescents. He wrote that this type of extrapolation from older populations to younger adolescents had been done in clinical trials for both prescription and OTC drug approvals and that this practice was incorporated into the Pediatric Research Equity Act (PREA)—the law authorizing FDA to require pediatric studies in certain defined circumstances.[49] According to PREA, if the disease and the effects of the drug are "sufficiently similar" between adult and pediatric populations, it can be concluded that the effectiveness can be extrapolated from "adequate and well-controlled studies in adults" usually in conjunction with supplemental studies in pediatric populations. In addition, PREA provides that studies may not be necessary for all pediatric age groups, if data from one age group can be extrapolated to another.

Members of the joint advisory committee expressed similar conclusions to those of FDA review officials earlier at the public meeting in December 2003. During the public meeting, committee members voted 27 to 1 that the actual use study data were generalizable to the overall population of OTC users, including adolescents.

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[49] See 21 U.S.C. § 355c(a)(2)(B).

Plan B Decision Was Not Typical of Other Proposed Prescription-to-OTC Switch Decisions

The decision to not approve the Plan B OTC switch application was not typical of the other 67 proposed prescription-to-OTC switch decisions made from 1994 through 2004. The decision of the Plan B application stands out from these other OTC switch applications for two reasons: it was the only decision that was not approved after the members of the joint advisory committee voted to recommend approval of the application, and the action letter was signed by the Acting Director of CDER instead of the directors of the offices where the application was reviewed.

Plan B Was the Only Prescription-to-OTC Switch Decision from 1994 through 2004 That Was Not Approved after the Joint Advisory Committee Voted to Recommend Approval of the Application

From 1994 through 2004, Plan B was the only prescription-to-OTC switch decision that was not approved after the joint advisory committee voted to recommend approval of the application. FDA advisory committees considered 23 OTC switch applications during this period; the Plan B OTC switch application was the only 1 of those 23 that was not approved after the joint advisory committee voted to recommend approval of the application. In addition, there has been only 1 other decision for an OTC switch application that did not follow the recommendations of the joint advisory committee. This other OTC switch application, for the drug Aleve, was approved for OTC status by FDA in 1994, although the joint advisory committee opposed the switch. The NDAC met jointly with the Arthritis Drugs Advisory Committee to discuss the OTC switch application for Aleve in June 1993 and recommended that the application not be approved. Following this meeting, the sponsor made changes to address the joint advisory committee's concerns, and as a result of these changes, FDA decided to approve the application.[50]

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[50] Reasons that the joint advisory committee gave for the recommendation against the OTC switch included that the dose was too high, the labeling for people over 65 years of age was incorrect, and no additional labeling was included for children regarding the side effect of photosensitivity.

Plan B Was the Only Prescription-to-OTC Switch Decision from 1994 through 2004 in Which the Action Letter Was Signed by the Director of CDER

From 1994 through 2004, 94 action letters were issued during the review processes for the 68 prescription-to-OTC switch applications, and only 1 action letter—the not-approvable letter for Plan B—was signed by the Director, in this case the Acting Director, of CDER. Given that Plan B was a first-in-a-class drug, the Directors of the Offices of Drug Evaluation III and V would normally jointly sign the action letter. The Plan B application was 1 of 68 proposed OTC switch applications decided by FDA from 1994 through 2004, and 14 of those 68 applications, including the Plan B application, were issued not-approvable letters. Eight of those 14 applications were eventually approved. Plan B was the only contraceptive or emergency contraceptive proposed for an OTC switch during this period. Thirty-eight OTC switch applications, including Plan B, were for the same dose, population, and indication, and all but 3 applications were eventually approved.

There Are No Age-Related Restrictions for Safety Reasons for Any FDA-Approved Contraceptives

According to the Deputy Director of the Office of New Drugs, there are no age-related marketing restrictions for any FDA-approved contraceptives, and FDA has not required any pediatric studies. Condoms and spermicides are available to anyone OTC, while intrauterine devices; diaphragms; cervical caps; and hormonal methods of contraception, including ECPs, are available to anyone with a prescription. For hormonal contraceptives, FDA has assumed that suppression of ovulation is the same in all postmenarcheal females, regardless of age. The Deputy Director of the Office of New Drugs told us that all birth control pills, including ECPs, contain the following class labeling: "Safety and effectiveness of [trade name] have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated."

FDA officials from the Office of New Drugs explained that for an OTC switch, the safety and effectiveness issues have already been addressed during the initial approval process for the drug to become a prescription drug. For an OTC switch application, the review process is primarily focused on whether the drug meets the OTC switch criteria, specifically whether it is safe and effective for use in self-medicating.[51]

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[51] In its technical comments on the draft of this report, FDA said that it also considers age in the labeling of OTC drug products. For example, FDA stated that there are many OTC drugs that have labels with dosing instructions based on age.

There were no safety issues that would require age-related restrictions that were identified with the original NDA for prescription Plan B. FDA approved this application upon determining that Plan B met the statutory standards of safety and effectiveness, manufacturing and controls, and labeling. The original NDA for Plan B for use as an emergency contraceptive contained an extensive safety database that included controlled trials and literature on over 15,000 women.[52] The label for prescription Plan B makes no age distinctions about the pharmacological processes of the drug, and prescription Plan B is available to anyone with a prescription.

Agency Comments and Our Evaluation

FDA reviewed a draft of this report and provided comments, which are reprinted in appendix VI. FDA also provided technical comments, which we incorporated as appropriate.

In its comments, FDA disagreed with our finding that three aspects of its decision process for the May 2004, Plan B OTC switch application were unusual. First, FDA said that the involvement of high-level management in the Plan B decision was not as unusual as the draft report found. FDA commented that the Director of CDER is ultimately responsible for all decisions made within CDER, and that the Director of CDER is regularly involved in regulatory decisions that are not routine, including those that involve controversial issues. FDA also commented that the Director of CDER typically discusses high-profile and controversial regulatory decisions with officials within the Office of the Commissioner.

While we agree with FDA that the Director of CDER and other high-level officials generally are more likely to become directly involved in high-profile regulatory decisions and noted that in the draft of the report, we found that this level of involvement is unusual for OTC switch applications. The other examples of high-level management involvement given to us by FDA officials during the course of our work involved decisions about the marketing of prescription drugs. Also, it was unusual for the Acting Director of CDER to inform FDA's review staff that it had been determined that the Plan B decision would be made by high-level management. The Acting Director did so on January 15, 2004, before the review staff had completed their reviews of the application.

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[52] The database included trials conducted in the United States and other countries. Women in the study were above the age of consent for their own countries.

Second, FDA took issue with what it characterized as the tone of our discussion about when the decision was made to deny the Plan B OTC switch application. FDA commented that discussions about alternative regulatory actions ordinarily occur in the course of decision making within CDER and that it is inaccurate to conclude that a decision to deny the application was made several months before the not-approvable letter was issued. However, the draft report did not assert that a decision was actually made several months before the letter was issued. Rather, it accurately noted that FDA officials gave us conflicting accounts of when the not-approvable decision was made. The Director and Deputy Director of the Office of New Drugs and other officials told us that they were informed during December 2003 and January 2004 that the application would not be approved. The Acting Director of CDER denied this, and we reported that his rationale for the not-approvable decision was not fully developed until early May 2004.

Third, FDA disagreed with our finding that the Acting Director's rationale for denying the application was novel and did not follow FDA's traditional practices. FDA commented that the Acting Director's focus on the potential implications to the sexual behavior of adolescent women of approving the Plan B OTC switch application was appropriate and consistent with FDA's treatment of other OTC switch applications.

In response to this comment, we have revised the report to more clearly describe the reasons for our finding. We found that the Acting Director's rationale was novel because it explicitly considered the differing levels of cognitive maturity of adolescents of different ages, and that because of the Acting Director's views about these cognitive maturity differences, he concluded that it was inappropriate to extrapolate data related to risky sexual behavior from older to younger adolescents. In his May 6, 2004, memorandum, the Acting Director stated that "Because of these large developmental differences, I believe that it is very difficult to extrapolate data on behavior from older to younger ages." The Acting Director acknowledged that considering adolescents' cognitive development as a rationale for a not-approvable decision was unprecedented for an OTC switch application. In addition, other FDA officials told us that the agency had not previously considered whether younger adolescents would use a product differently than older adolescents. For example, the Director of the Office of New Drugs told us that it was "atypical" to raise the question of maturity during a drug review and that FDA has traditionally extrapolated findings from older to younger adolescents. Furthermore, in his April 22, 2004, memorandum, the Director of the Office of New Drugs said that "the Agency has a long history of extrapolating findings from clinical trials in older patients to adolescents in both prescription and nonprescription approvals."

In addition, FDA disagreed with our statement in the draft report that the Directors of the Offices of Drug Evaluation III and V and the Director of the Office of New Drugs refused to sign the not-approvable letter. We used the term "refused" in the draft report because, in our interviews with them, all three of the directors told us that they did not agree with the not-approvable decision and did not sign the action letter, and one of the directors told us that she had been given an opportunity to sign the letter and refused to do so. However, in its comments, FDA said that the directors were not asked to sign the action letter because it was known that they disagreed with the Acting Director's decision. We have revised the report to reflect this.

In its technical comments, FDA asked us to emphasize that safety concerns regarding OTC use of drug would not be raised for prescription products because of the involvement of health practitioners. The draft report noted that prescription drugs are drugs that are safe for use only under supervision of a health care practitioner and that approved prescription drugs that no longer require such supervision may be marketed OTC.

We are sending copies of this report to the Acting Commissioner of the Food and Drug Administration and other interested parties. We will also provide copies to others upon request. In addition, the report will be available at no charge on GAO's Web site at http://www.gao.gov.

If you or your staffs have any questions about this report, please contact me at (202) 512-7119 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix VII.

Marcia Crosse

Marcia Crosse
Director, Health Care

List of Requesters

The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Carl Levin
Ranking Minority Member
Permanent Subcommittee on Investigations
Committee on Governmental Affairs
United States Senate

The Honorable John D. Dingell
Ranking Minority Member
Committee on Energy and Commerce
House of Representatives

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
House of Representatives

The Honorable Jeff Bingaman
The Honorable Barbara Boxer
The Honorable Maria Cantwell
The Honorable Hillary Rodham Clinton
The Honorable Jon Corzine
The Honorable Mark Dayton
The Honorable Christopher J. Dodd
The Honorable Richard J. Durbin
The Honorable Tom Harkin
The Honorable Daniel K. Inouye
The Honorable James M. Jeffords
The Honorable Frank R. Lautenberg
The Honorable Barbara A. Mikulski
The Honorable Patty Murray
The Honorable Charles E. Schumer
The Honorable Debbie Stabenow
The Honorable Ron Wyden
United States Senate

The Honorable Tammy Baldwin
The Honorable Sherrod Brown
The Honorable Lois Capps
The Honorable Benjamin L. Cardin
The Honorable Joseph Crowley
The Honorable Susan A. Davis
The Honorable Lloyd Doggett
The Honorable Sam Farr
The Honorable Bob Filner
The Honorable Maurice D. Hinchey
The Honorable Rush D. Holt
The Honorable Michael M. Honda
The Honorable Barbara Lee
The Honorable Nita M. Lowey
The Honorable Carolyn B. Maloney
The Honorable Edward J. Markey
The Honorable James P. Moran, Jr.
The Honorable Jerrold Nadler
The Honorable Eleanor Holmes Norton
The Honorable Janice D. Schakowsky
The Honorable Louise M. Slaughter
The Honorable Hilda L. Solis
The Honorable Edolphus Towns
The Honorable Mark Udall
The Honorable Chris Van Hollen
The Honorable Diane E. Watson
The Honorable Lynn C. Woolsey
House of Representatives

Appendix I: Scope and Methodology

To examine how the decision was made to not approve the switch of Plan B from prescription to over-the-counter (OTC), we reviewed documents, such as the Plan B OTC switch action package related to the May 6, 2004, decision from the Food and Drug Administration (FDA). We examined documents produced by FDA, including official meeting minutes and the reviews of the Plan B OTC switch application from the Offices of Drug Evaluation III and V and the Office of New Drugs, related to the review of the Plan B OTC switch application. FDA officials told us that documentation was not available concerning some communications within FDA. It was not possible to determine whether such communications may have concerned the Plan B OTC switch application. However, we acquired sufficient information from other FDA documents and our interviews with FDA officials to fully address our objectives.

We interviewed FDA officials involved in the Plan B OTC switch application review, including officials from the Office of Drug Evaluation III, Office of Drug Evaluation V, Office of New Drugs, and Office of Drug Safety. We also interviewed the Acting Director of the Center for Drug Evaluation and Research (CDER), the Acting Deputy Commissioner for Operations, and the Director of the Office of Women's Health. We interviewed members of FDA's advisory committees that met jointly to discuss the Plan B OTC switch application—the Nonprescription Drugs Advisory Committee (NDAC) and the Advisory Committee for Reproductive Health Drugs (ACRHD)—and reviewed the transcripts of the meeting. In addition, we interviewed officials from Barr Pharmaceuticals, Inc., the company currently sponsoring the Plan B application for the prescription-to-OTC switch, and Women's Capital Corporation (WCC), the original sponsor of the Plan B OTC switch application.

To examine how the Plan B decision compares to the decisions for other proposed prescription-to-OTC switches made from 1994 through 2004, we examined the recommendations of the joint advisory committee and if they were followed for Plan B and the proposed OTC switch drugs that were decided from 1994 through 2004. We reviewed action letters and interviewed FDA officials and review staff as well as other outside experts involved with the Plan B OTC switch application. We also interviewed officials from the Consumer Healthcare Products Association (the association representing OTC drug manufacturers) about the prescription-to-OTC switch process.

To determine if there were age-related marketing restrictions for prescription Plan B and other prescription and OTC contraceptives, we reviewed FDA documents and interviewed FDA officials and review staff regarding safety concerns for prescription Plan B and the safety concerns for other prescription and OTC contraceptives. We also interviewed representatives from the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, Concerned Women for America, and the Planned Parenthood Federation of America, Inc., regarding safety concerns for Plan B and other contraceptives.

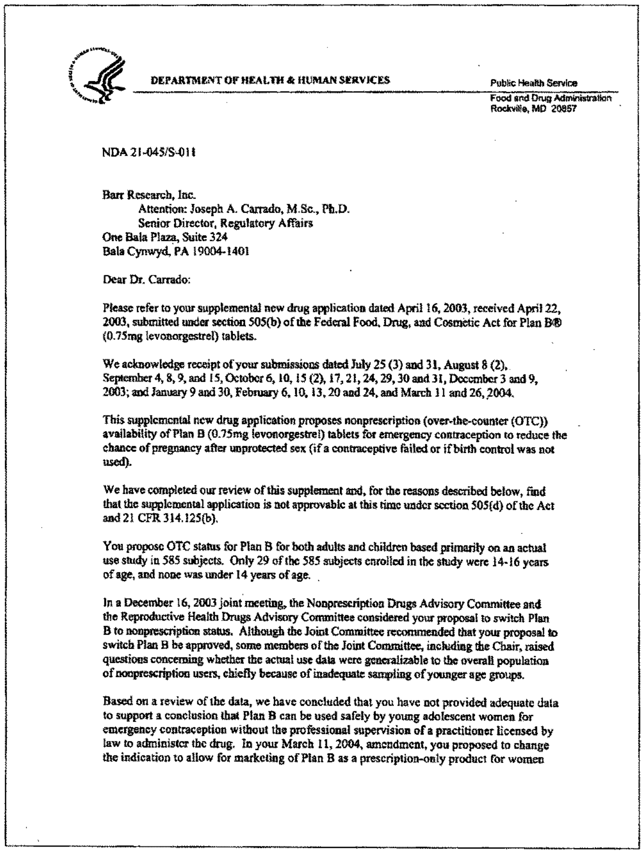
When the source of evidence we cited is from an interview, we identified the respondent's title and FDA office. Whenever possible, we reviewed documents to verify testimonial evidence from FDA officials. When this was not possible, we attempted to corroborate testimonial evidence by interviewing multiple people about the information we obtained. In situations where there was no concurrence among the interviewees, we presented all the information provided.

Minutes of the internal FDA meetings discussed in this report were written either by a staff member within the Office of Drug Evaluation III or by the Executive Secretariat within the Office of the Commissioner. For meeting minutes written by the office staff member, attendees either reviewed or concurred with the minutes and documented this by including their names at the end of the minutes. For summaries written by the Executive Secretariat, there was no documentation of a review or of concurrence by attendees included with these summaries. FDA officials told us that summaries from meetings within the Office of the Commissioner were not reviewed or concurred with by attendees.

To verify data we received from FDA regarding proposed prescription-to-OTC switch decisions made from 1994 through 2004 and the outcomes of advisory committee meetings for these drugs, we compared FDA's data with prescription-to-OTC switch data obtained from the Consumer Healthcare Products Association on OTC drug switches.

Our work examined only events and communications within FDA and between FDA and the Plan B sponsors; we did not consider any communications that may have occurred between FDA officials and other executive agencies. Our work examined only FDA's actions prior to the May 6, 2004, not-approvable letter, and we did not examine any aspects of FDA's subsequent deliberations about Plan B. We conducted our work from September 2004 through November 2005 in accordance with generally accepted government auditing standards.

Appendix II: Not-Approvable Letter for the Prescription-to-OTC Switch Application of Plan B, May 6, 2004



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-045/S-011

Barr Research, Inc.
Attention: Joseph A. Carrado, M.Sc., Ph.D.
Senior Director, Regulatory Affairs
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004-1401

Dear Dr. Carrado:

Please refer to your supplemental new drug application dated April 16, 2003, received April 22, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B® (0.75mg levonorgestrel) tablets.

We acknowledge receipt of your submissions dated July 25 (3) and 31, August 8 (2), September 4, 8, 9, and 15, October 6, 10, 15 (2), 17, 21, 24, 29, 30 and 31, December 3 and 9, 2003; and January 9 and 30, February 6, 10, 13, 20 and 24, and March 11 and 26, 2004.

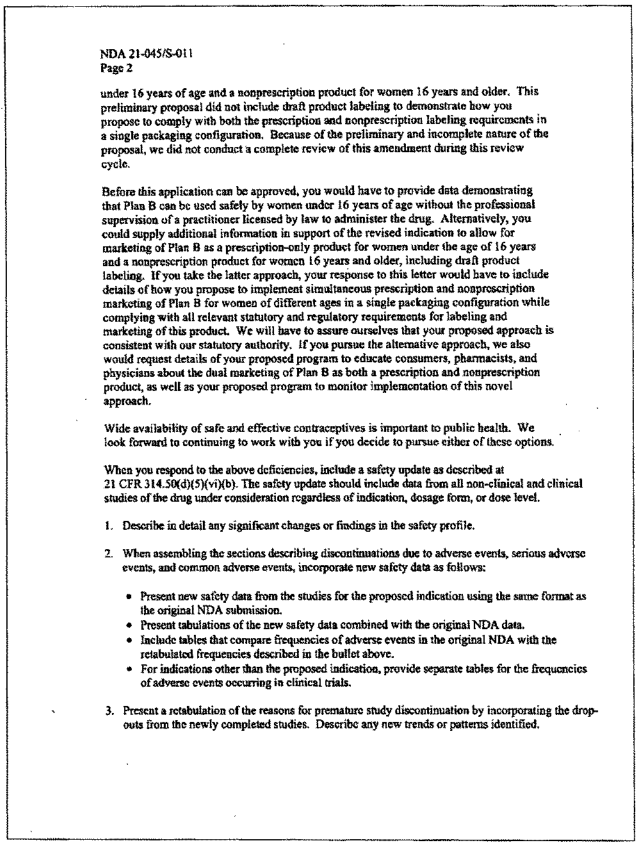
This supplemental new drug application proposes nonprescription (over-the-counter (OTC)) availability of Plan B (0.75mg levonorgestrel) tablets for emergency contraception to reduce the chance of pregnancy after unprotected sex (if a contraceptive failed or if birth control was not used).

We have completed our review of this supplement and, for the reasons described below, find that the supplemental application is not approvable at this time under section 505(d) of the Act and 21 CFR 314.125(b).

You propose OTC status for Plan B for both adults and children based primarily on an actual use study in 585 subjects. Only 29 of the 585 subjects enrolled in the study were 14-16 years of age, and none was under 14 years of age.

In a December 16, 2003 joint meeting, the Nonprescription Drugs Advisory Committee and the Reproductive Health Drugs Advisory Committee considered your proposal to switch Plan B to nonprescription status. Although the Joint Committee recommended that your proposal to switch Plan B be approved, some members of the Joint Committee, including the Chair, raised questions concerning whether the actual use data were generalizable to the overall population of nonprescription users, chiefly because of inadequate sampling of younger age groups.

Based on a review of the data, we have concluded that you have not provided adequate data to support a conclusion that Plan B can be used safely by young adolescent women for emergency contraception without the professional supervision of a practitioner licensed by law to administer the drug. In your March 11, 2004, amendment, you proposed to change the indication to allow for marketing of Plan B as a prescription-only product for women



NDA 21-045/S-011
Page 2

under 16 years of age and a nonprescription product for women 16 years and older. This preliminary proposal did not include draft product labeling to demonstrate how you propose to comply with both the prescription and nonprescription labeling requirements in a single packaging configuration. Because of the preliminary and incomplete nature of the proposal, we did not conduct a complete review of this amendment during this review cycle.

Before this application can be approved, you would have to provide data demonstrating that Plan B can be used safely by women under 16 years of age without the professional supervision of a practitioner licensed by law to administer the drug. Alternatively, you could supply additional information in support of the revised indication to allow for marketing of Plan B as a prescription-only product for women under the age of 16 years and a nonprescription product for women 16 years and older, including draft product labeling. If you take the latter approach, your response to this letter would have to include details of how you propose to implement simultaneous prescription and nonprescription marketing of Plan B for women of different ages in a single packaging configuration while complying with all relevant statutory and regulatory requirements for labeling and marketing of this product. We will have to assure ourselves that your proposed approach is consistent with our statutory authority. If you pursue the alternative approach, we also would request details of your proposed program to educate consumers, pharmacists, and physicians about the dual marketing of Plan B as both a prescription and nonprescription product, as well as your proposed program to monitor implementation of this novel approach.

Wide availability of safe and effective contraceptives is important to public health. We look forward to continuing to work with you if you decide to pursue either of these options.

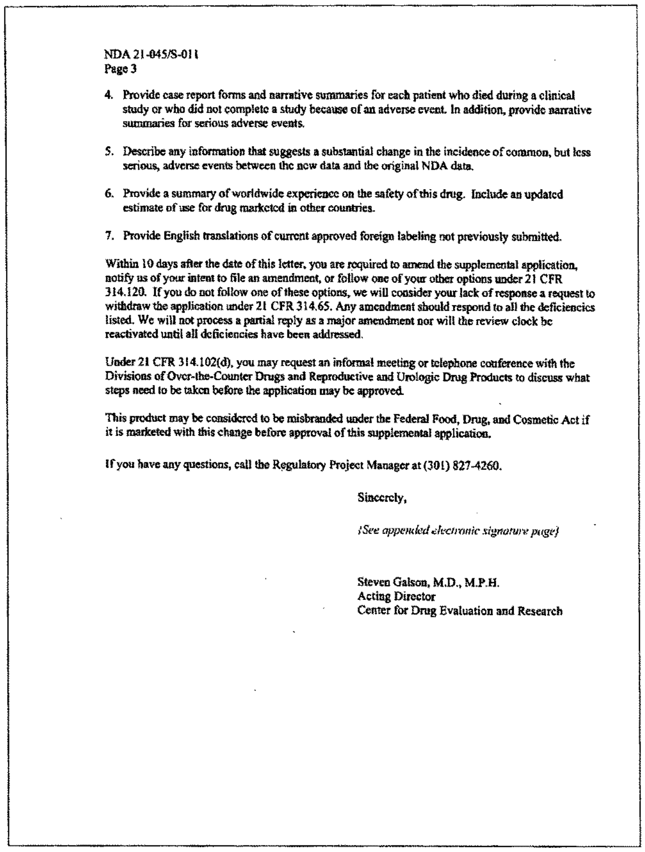
When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.



NDA 21-045/S-011
Page 3

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Divisions of Over-the-Counter Drugs and Reproductive and Urologic Drug Products to discuss what steps need to be taken before the application may be approved.

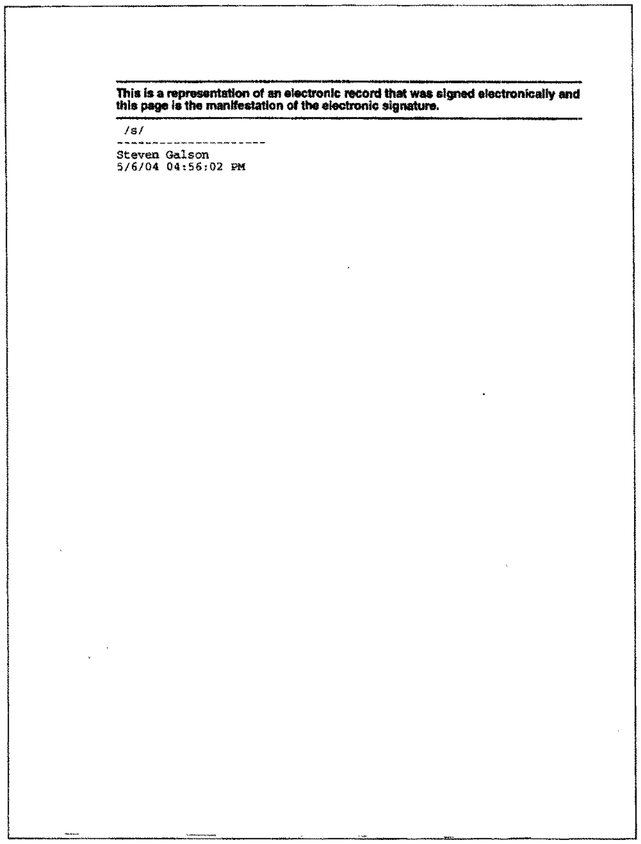
This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call the Regulatory Project Manager at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Steven Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research



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Steven Galson
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Appendix III: Timeline of Major Plan B Events Related to the Initial OTC Switch Application

Date	Event
February 25, 1997	A notice in the *Federal Register* stated that the FDA Commissioner had concluded that certain combined oral contraceptives are safe and effective for use as emergency contraception and requested submission of a new drug application (NDA) for this use.
July 28, 1999	FDA approved Plan B as a prescription form of emergency contraception.
February 14, 2001	A citizens' petition for direct over-the-counter (OTC) access to Plan B was filed, requesting that FDA grant Plan B OTC status.
April 18, 2002	FDA review staff within the Office of Drug Evaluation III sent Women's Capital Corporation (WCC) a letter, denying its proposal that FDA request that it conduct pediatric studies on the use of prescription Plan B as an emergency contraceptive in exchange for extending the drug's marketing exclusivity for 6 months, as permitted under the Federal Food, Drug, and Cosmetic Act.[a] According to the letter to WCC and a memorandum by review staff within the Office of Drug Evaluation III, the proposed studies would have included a pharmacokinetic study and a safety study and would have used Plan B as an emergency contraceptive in subjects as young as 12 years of age. According to review staff within the Office of Drug Evaluation III, once a young female reached menarche, she was considered an adult for contraceptives and the condition for using an emergency contraceptive is not unique to the pediatric population. The letter concluded that trials could be conducted in the adult population and then extrapolated to the pediatric population.
May 28, 2002	A Center Director Informational Briefing was held in response to the citizens' petition, filed on February 14, 2001. Meeting attendees included the Center for Drug Evaluation and Research (CDER) Director and Deputy Director, the Director of Office of New Drugs, and review staff from the Offices of Drug Evaluation III and V.
June 5, 2002	A briefing for the Office of the Commissioner was held to discuss the expected application to switch Plan B to OTC. Attendees included the Deputy Commissioner,[b] the agency's Chief Counsel, the then Director of CDER, the Director of the Office of New Drugs, and review staff from the Offices of Drug Evaluation III and V. According to the executive summary of the briefing, issues discussed included (1) the political sensitivity of the application, (2) consumer understanding of the proposed nonprescription product label, (3) the results of actual use studies to adequately address safety issues, (4) the review status of the supplemental new drug application (sNDA) upon submission, and (5) regulatory issues.
July 10, 2002	The Director of CDER provided the Deputy Commissioner and FDA's Chief Counsel with materials on the safety of emergency contraception and its mechanism of action, which were requested at the June 5, 2002, briefing.
September 23, 2002	FDA officials within the Office of New Drugs and the Offices of Drug Evaluation III and V and the sponsor held a meeting in which FDA provided guidance on the Plan B OTC switch application, which was to be submitted. According to meeting minutes, agency officials and the sponsor discussed behavioral issues in adolescents and the possibility of a behind-the-counter option or a possible age restriction.[c]
April 16, 2003	WCC submitted an sNDA to FDA to allow Plan B to be sold OTC.
June 9, 2003	FDA review staff from the Office of Drug Evaluation III determined that the sNDA was fileable and accepted it for review. FDA set a Prescription Drug User Fee Act (PDUFA) goal date of February 22, 2004, to reach a decision on the application.[d]

Date	Event
August 22, 2003	A teleconference was held between review staff within Offices of Drug Evaluation III and V and the sponsor. According to minutes of this teleconference, review staff began working with the sponsor to prepare for the meeting of the joint advisory committee in December. Minutes also noted that FDA review staff suggested that the sponsor plan to address issues of age, literacy, or label comprehension regarding the administration of Plan B.
September 11, 2003	Review within the Office of Drug Evaluation V requested additional information on the label comprehension study results from WCC. According to the official request, review staff asked for information including results for each question asked in the label comprehension study based on literacy levels; details on what criteria were used to determine if a communication objective was met; and other specific points of clarification on how responses were scored.
September 26, 2003	A teleconference was held in which review staff within the Offices of Drug Evaluation III and V discussed the upcoming December 16, 2003, public meeting of its two advisory committees with WCC. According to teleconference minutes, review staff requested additional information on the labels used for the label comprehension and the actual use studies and on the label proposed for approval in the sNDA. Minutes also noted that WCC informed FDA that on September 23, 2003, a majority of its board voted to sell the marketing rights of Plan B to Barr Pharmaceuticals, Inc.
October 2003	Barr Pharmaceuticals, Inc., was finalizing the purchase of the marketing rights for Plan B from WCC and began to act as the agent for WCC for Plan B.
October 9, 2003	At the request of Barr Pharmaceuticals, Inc., a teleconference was held to discuss the upcoming joint public meeting of FDA's advisory committees. Meeting participants from FDA included review staff within the Offices of Drug Evaluation III and V. According to teleconference minutes, review staff asked Barr Pharmaceuticals, Inc., about possible age restrictions for use of Plan B. Minutes also noted that Barr Pharmaceuticals, Inc., said that it intended to offer its product to women as young as 15 years of age. Also, Barr Pharmaceuticals, Inc., agreed to explore and report back to FDA on behind-the-counter marketing and the implementation of age limitations on the sale of Plan B.
November 5, 2003	A reviewer within the Office of Drug Safety completed her review of the Plan B label comprehension study, which was initially submitted to review staff within the Office of Drug Evaluation III. According to the official memorandum on the review of the label comprehension study, the reviewer concluded that making the proposed changes to the Plan B label would likely result in acceptable levels of comprehension. Review staff within the Office of Drug Evaluation V told GAO they concurred with the reviewer's findings.
December 2, 2003	A meeting was held between FDA officials within the Office of New Drugs and the Offices of Drug Evaluation III and V and the sponsor. According to meeting minutes, FDA officials informed Barr Pharmaceuticals, Inc., that the agency may not be able to present a clear regulatory path for alternate OTC distribution mechanisms for Plan B in time for the December 16, 2003, public meeting.
December 10, 2003	A briefing for the Office of the Commissioner was held to discuss the upcoming public meeting of the Nonprescription Drugs Advisory Committee (NDAC) and Advisory Committee for Reproductive Health Drugs (ACRHD). FDA participants included the Commissioner, the Acting Director of CDER, the Director and Deputy Director of the Office of New Drugs, and review staff within the Office of Drug Safety and the Offices of Drug Evaluation III and V. According to the executive summary of the briefing, issues discussed included the sponsor's marketing and distribution plan and the effect making Plan B available OTC might have on consumers' behavior.
December 16, 2003	At a joint meeting of the NDAC and the ACRHD, members voted 23 to 4 to recommend approving the switch of Plan B from prescription to OTC.

Date	Event
December 2003/January 2004	The Director and the Deputy Director of the Office of New Drugs told GAO they were told by the Acting Deputy Commissioner for Operations[a] and the Acting Director of CDER that the Plan B application could not be approved. These officials said they were told that this direction came from the Office of the Commissioner. The Acting Deputy Commissioner for Operations and the Acting Director of CDER told GAO they did not say this.
January 15, 2004	A meeting was held between officials within the Office of the CDER Director and review staff within the Offices of Drug Evaluation III and V about the Office of the Commissioner's position on the acceptability of the Plan B OTC switch application. According to meeting minutes, the Acting Director of CDER said that a not-approvable decision was recommended by the Office of the Commissioner based on the need for more data to more clearly establish appropriate use in younger adolescents, the need to develop a restricted distribution plan, or both. Meeting minutes also indicated that review staff also informed the Acting Director that their reviews were not yet completed and that there were additional data regarding adolescent use of Plan B. It was then agreed that review staff would complete their reviews and collect the additional data and present them to the Commissioner and the Acting Director of CDER some time in February. Review staff within both Offices of Drug Evaluation III and V later noted in their completed reviews of the Plan B OTC switch application that they were told at this meeting that the decision on the Plan B application would be made at a level higher than the offices of drug evaluation.
January 16, 2004	A teleconference was held between review staff from the Office of Drug Evaluation V and the sponsor. According to meeting minutes, review staff informed the sponsor that a meeting was held with CDER management, including the Acting Director of CDER and the Director and Deputy Director of the Office of New Drugs, in which "some issues" were raised that would require review staff to "provide additional information and have additional discussions with CDER upper management." Minutes also noted that review staff told the sponsor they would not be discussing labeling revisions at that time and that they had been instructed by CDER management to complete their written reviews regarding the OTC switch application.
January 21, 2004	A memorandum from the Director of Office of Drug Evaluation V indicated that she was in agreement with the favorable assessment of review staff and the majority votes by members of the joint advisory committee. Her memorandum concluded that adequate data had been submitted to approve Plan B for OTC marketing with certain product-labeling modifications—such as strengthening the message that Plan B is not for regular contraceptive use—included to address concerns raised at the public meeting and in the agency's reviews.
January 23, 2004	A meeting was held between FDA officials within the Office of New Drugs and the Offices of Drug Evaluation III and V and Barr Pharmaceuticals, Inc./WCC. According to meeting minutes, FDA officials told the sponsor that the decision on the application would be made at a level higher than the Offices of Drug Evaluation. The Director of the Office of New Drugs told the sponsor that such a high-level decision was not typical of CDER's procedures for drug approvals. The minutes also noted that review staff within the Offices of Drug Evaluation were in the process of completing their reviews and would forward them with their final recommendations to high-level management. Meeting minutes also indicated that FDA officials told the sponsor that they would need to request a meeting directly with the Office of the Center Director or the Office of New Drugs to understand high-level management's concerns. In addition, meeting minutes noted that FDA officials told the sponsor that the Office of the Commissioner and the Acting Director of CDER had raised concerns as to whether there were adequate data to establish that minors (i.e., those under 18 years of age) would use Plan B appropriately in the absence of a learned intermediary. Potential options that were suggested from FDA and CDER management included the possible need to (1) collect additional data, perhaps from another actual use study targeted to minors, or (2) to impose an age restriction on the OTC sale of the product.

Date	Event
February 2, 2004	Review staff within the Office of Drug Evaluation III requested that the sponsor reanalyze the adolescent data of the Plan B actual use study. According to the official request, staff asked for a "[s]ummary presentation of the Actual Use data from the participants in the less than 18 years of age subset, including comparisons to the older subset within the study."
February 13, 2004	FDA confirmed that it had extended the PDUFA goal date for a decision on the Plan B OTC switch application for 90 days due to the submission of the requested adolescent data from the actual use study by the sponsor. The extended PDUFA goal date was May 21, 2004.
February 18, 2004	A briefing was held during which review staff within Offices of Drug Evaluation III and V presented their analysis of additional summary data to the Commissioner on the use and behavior of adolescents in association with increased access to emergency contraceptive pills. Other attendees included the Acting Deputy Commissioner for Operations and the Acting Director of CDER. According to meeting minutes, included in the presentation were the review staff's recommendations that Plan B have an OTC marketing status without restriction. The meeting minutes also noted that the Commissioner raised concerns regarding adolescents, including the potential for changes in future contraceptive behaviors and the potential benefits of counseling from a learned intermediary for younger adolescents. In addition, the meeting minutes noted that CDER was directed by the Commissioner to work with the sponsor on a marketing plan to limit the availability of Plan B in an OTC setting and to consider the most appropriate ages that should have OTC access restricted. The Commissioner requested a "rapid action" on the application.
February 19, 2004	Review staff within the Offices of Drug Evaluation III and V met with the Acting Deputy Commissioner for Operations, the Acting Director of CDER, and the Director and the Deputy Director of the Office of New Drugs. According to a reviewer's memorandum, in part, during this meeting, the Acting Deputy Commissioner for Operations expressed her and the Commissioner's concerns regarding adolescents and the potential for adverse behaviors resulting from increased access to Plan B. The Acting Director of CDER concurred with these concerns.
February 22, 2004	This was the original PDUFA goal date for the initial Plan B OTC switch application.
February 26, 2004	Barr Pharmaceuticals, Inc., completed acquisition of the marketing rights for Plan B from WCC.
March 11, 2004	Barr Pharmaceuticals, Inc., submitted an amendment to its sNDA, proposing a dual-marketing strategy, making Plan B OTC for women 16 years of age and older and prescription only for women under 16 years of age.
April 2, 2004	The Deputy Director of the Office of Drug Evaluation III completed her review of the Plan B OTC switch application and recommended that Plan B be approved for use as an emergency contraceptive in the OTC setting without age restriction. The review concluded there were sufficient data on the safety and effectiveness of Plan B to approve its use in the OTC setting.
April 22, 2004	The Director of the Office of New Drugs issued his review of the Plan B application and concurred with the recommendations of the offices of drug evaluation that the sponsor had provided adequate data to demonstrate that Plan B could be safely, effectively, and appropriately used by women of childbearing potential for the indication of emergency contraception without a prescription. He recommended that this application be approved to permit availability of Plan B without a prescription and without age restriction.
May 2, 2004	The Acting Director of CDER contacted the Director of the Office of Pediatric Therapeutics, within the Office of the Commissioner, via e-mail requesting assistance on language regarding cognitive development among adolescents. According to internal FDA e-mails, the Director of the Office of Pediatric Therapeutics responded that she would consult with another official with a background in developmental pediatrics and would follow up with "behavioral science information as to why one cannot extrapolate decision making on safety issues" from older populations to younger adolescents.

Date	Event
May 3, 2004	According to internal FDA e-mails, the Director of the Office of Pediatric Therapeutics provided the Acting Director of CDER with information on brain development and the maturation of higher-order thinking among adolescents 10 years to 21 years of age. In her e-mail to the Acting Director, the Director of the Office of Pediatric Therapeutics included the statement that "[d]uring early adolescence (10-13) there is an emergence of impulsive behavior without the cognitive ability to understand the etiology of their behavior."
May 5, 2004	According to teleconference minutes, the Acting Director of CDER called Barr Pharmaceuticals, Inc., officials to inform them of the not-approvable action and asked permission to release the not-approvable letter. According to FDA regulations, without consent of the sponsor, the agency cannot publicly release data or information contained in an application before an approval letter is issued.[f] Minutes noted that the Acting Director told sponsor officials that (with their permission) he would conduct a press interview to discuss the not-approvable action and the staff's disagreement with the not-approvable action would be acknowledged publicly.
May 6, 2004	FDA issued a not-approvable letter, denying Plan B OTC marketing status, citing a lack of adequate data regarding safe use among younger adolescents. The letter also stated that FDA was not able to conduct a complete review of the dual-marketing strategy in the amendment to the sNDA because of the absence of the draft product labeling describing how Barr Pharmaceuticals, Inc., would comply with both the prescription and OTC labeling requirements in a single package.

Source: GAO analysis of FDA data.

[a] See 21 U.S.C. § 355a(b), (c). FDA may request that manufacturers of new or already-marketed drugs conduct studies of their drugs in pediatric populations where it believes that such studies will lead to additional health benefits. Studies completed in accordance with FDA requirements entitle the manufacturer to an additional 6 months of marketing exclusivity. In its technical comments on the draft of this report, FDA stated that it did not ask for pediatric data for the prescription version of Plan B because the product's physiological effects are the same in younger and older women, and because a health care practitioner is involved in dispensing prescription drugs.

[b] On September 23, 2005, the Commissioner of FDA, who was appointed on July 18, 2005, resigned from his position. He held the title of Deputy Commissioner from February 24, 2002, until March 26, 2004, when he was named Acting Commissioner. Because he was Deputy Commissioner during most of the time covered by this report—for those events associated with the initial Plan B OTC switch application through the May 6, 2004, decision—we use the title of Deputy Commissioner for him in this report.

[c] Behind-the-counter is defined as a classification of drug products that do not require a prescription but are also unlike OTC products in that there is a measure of clinical oversight in their use. For behind-the-counter products, pharmacists are able to intervene by advising patients on the product's proper use and associated risks and by referring them to their physicians when appropriate. See Robert I. Field, "Support Grows for a Third Class of 'Behind-the-Counter' Drugs," *Pharmacy and Therapeutics*, vol. 30, no.5 (2005): 260-261.

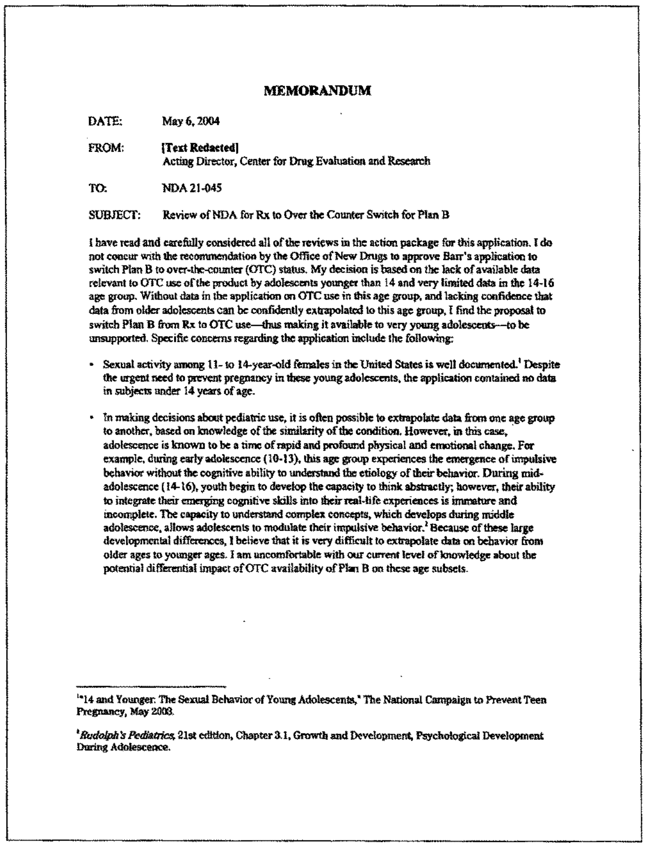
[d] FDA, in collaboration with various stakeholders, including representatives from consumer, patient, and health care provider groups and the pharmaceutical and biotechnology industries, has developed performance goals for the time to complete the review of an application submitted to the agency, which have been incorporated by reference into PDUFA.

[e] The Acting Deputy Commissioner for Operations was the Director of CDER when the initial Plan B OTC switch application was submitted in April 2003. She told GAO that she became the Acting Deputy Commissioner for Operations in March 2004, and that her role in the review of the initial Plan B OTC switch application was as a consultant to the Acting CDER Director.

[f] See 21 C.F.R. § 314.430(d)(1).

Appendix IV: Acting Director of CDER's Official Memorandum Explaining His Not-Approvable Decision, May 6, 2004

The following is the official memorandum submitted to the record by the Acting Director of CDER to explain his decision on the initial Plan B OTC switch application. GAO has redacted information identifying specific persons as well as information not directly related to the review of the initial Plan B application.



MEMORANDUM

DATE: May 6, 2004

FROM: **[Text Redacted]**
Acting Director, Center for Drug Evaluation and Research

TO: NDA 21-045

SUBJECT: Review of NDA for Rx to Over the Counter Switch for Plan B

I have read and carefully considered all of the reviews in the action package for this application. I do not concur with the recommendation by the Office of New Drugs to approve Barr's application to switch Plan B to over-the-counter (OTC) status. My decision is based on the lack of available data relevant to OTC use of the product by adolescents younger than 14 and very limited data in the 14-16 age group. Without data in the application on OTC use in this age group, and lacking confidence that data from older adolescents can be confidently extrapolated to this age group, I find the proposal to switch Plan B from Rx to OTC use—thus making it available to very young adolescents—to be unsupported. Specific concerns regarding the application include the following:

- Sexual activity among 11- to 14-year-old females in the United States is well documented.[1] Despite the urgent need to prevent pregnancy in these young adolescents, the application contained no data in subjects under 14 years of age.
- In making decisions about pediatric use, it is often possible to extrapolate data from one age group to another, based on knowledge of the similarity of the condition. However, in this case, adolescence is known to be a time of rapid and profound physical and emotional change. For example, during early adolescence (10-13), this age group experiences the emergence of impulsive behavior without the cognitive ability to understand the etiology of their behavior. During mid-adolescence (14-16), youth begin to develop the capacity to think abstractly; however, their ability to integrate their emerging cognitive skills into their real-life experiences is immature and incomplete. The capacity to understand complex concepts, which develops during middle adolescence, allows adolescents to modulate their impulsive behavior.[2] Because of these large developmental differences, I believe that it is very difficult to extrapolate data on behavior from older ages to younger ages. I am uncomfortable with our current level of knowledge about the potential differential impact of OTC availability of Plan B on these age subsets.

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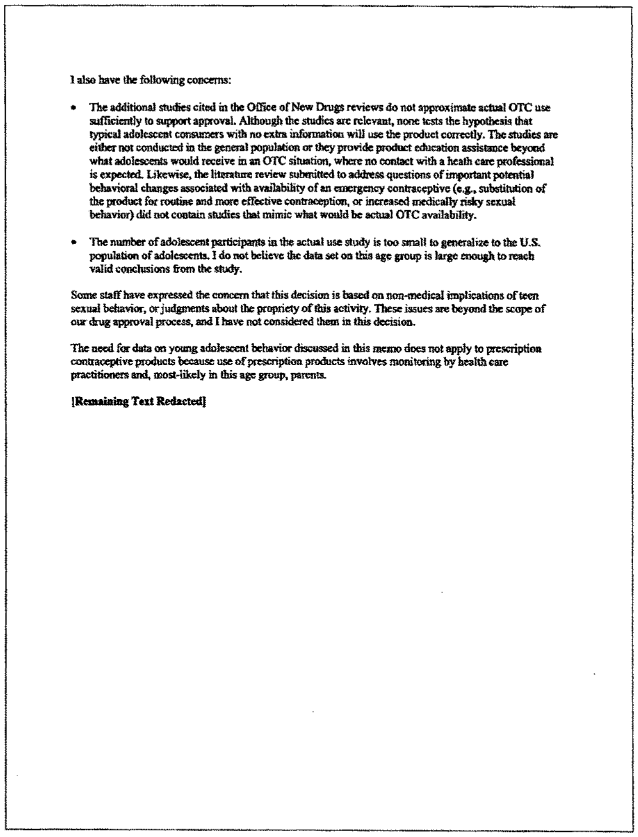
[1] "14 and Younger: The Sexual Behavior of Young Adolescents," The National Campaign to Prevent Teen Pregnancy, May 2003.

[2] *Rudolph's Pediatrics*, 21st edition, Chapter 3.1, Growth and Development, Psychological Development During Adolescence.



I also have the following concerns:

- The additional studies cited in the Office of New Drugs reviews do not approximate actual OTC use sufficiently to support approval. Although the studies are relevant, none tests the hypothesis that typical adolescent consumers with no extra information will use the product correctly. The studies are either not conducted in the general population or they provide product education assistance beyond what adolescents would receive in an OTC situation, where no contact with a heath care professional is expected. Likewise, the literature review submitted to address questions of important potential behavioral changes associated with availability of an emergency contraceptive (e.g., substitution of the product for routine and more effective contraception, or increased medically risky sexual behavior) did not contain studies that mimic what would be actual OTC availability.

- The number of adolescent participants in the actual use study is too small to generalize to the U.S. population of adolescents. I do not believe the data set on this age group is large enough to reach valid conclusions from the study.

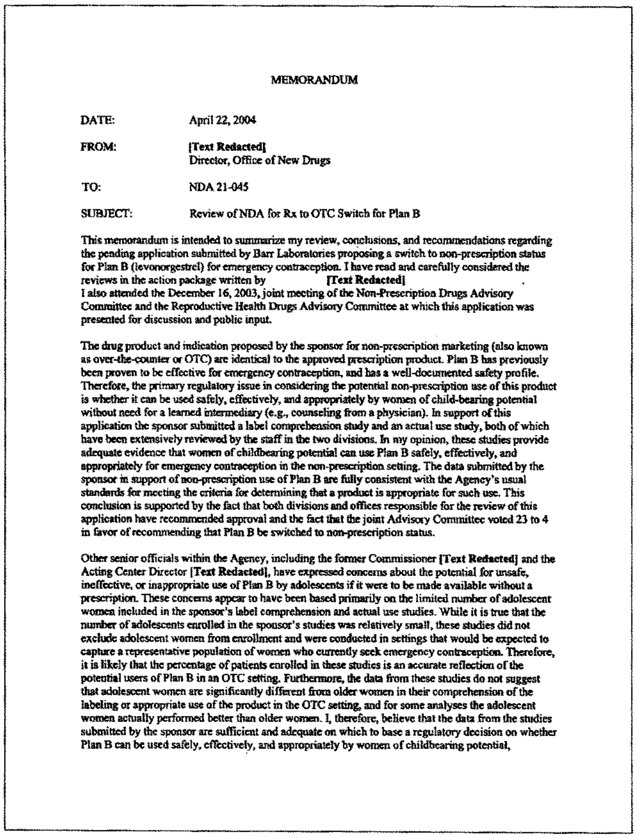
Some staff have expressed the concern that this decision is based on non-medical implications of teen sexual behavior, or judgments about the propriety of this activity. These issues are beyond the scope of our drug approval process, and I have not considered them in this decision.

The need for data on young adolescent behavior discussed in this memo does not apply to prescription contraceptive products because use of prescription products involves monitoring by health care practitioners and, most-likely in this age group, parents.

[Remaining Text Redacted]

Appendix V: Director of the Office of New Drugs' Official Memorandum on His Decision on the Plan B Application, April 22, 2004

The following is the official memorandum submitted to the record by the Director of the Office of New Drugs to explain his decision on the initial Plan B OTC switch application. GAO has redacted information identifying specific persons as well as information not directly related to the review of the initial Plan B application.



MEMORANDUM

DATE: April 22, 2004

FROM: **[Text Redacted]**
Director, Office of New Drugs

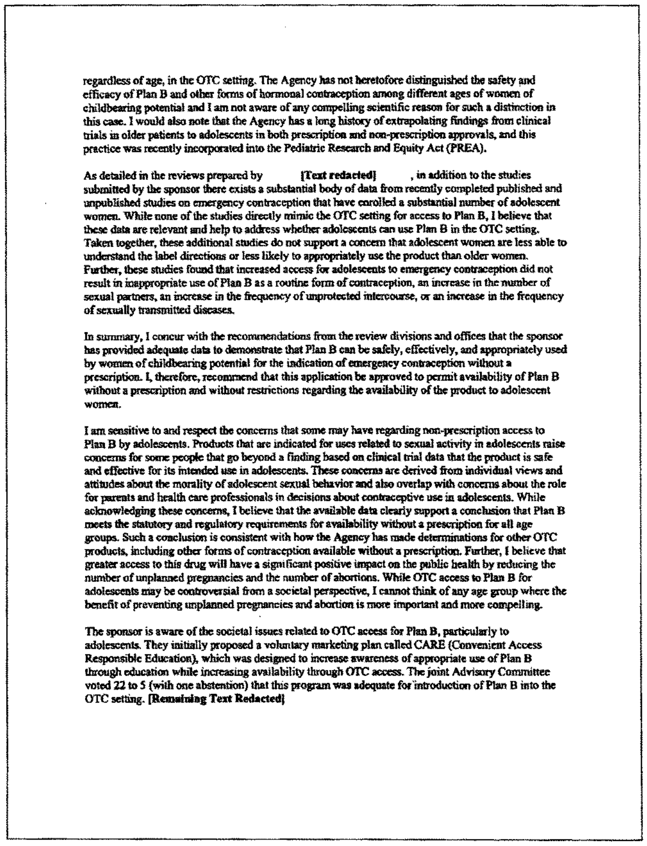
TO: NDA 21-045

SUBJECT: Review of NDA for Rx to OTC Switch for Plan B

This memorandum is intended to summarize my review, conclusions, and recommendations regarding the pending application submitted by Barr Laboratories proposing a switch to non-prescription status for Plan B (levonorgestrel) for emergency contraception. I have read and carefully considered the reviews in the action package written by **[Text Redacted]** .
I also attended the December 16, 2003, joint meeting of the Non-Prescription Drugs Advisory Committee and the Reproductive Health Drugs Advisory Committee at which this application was presented for discussion and public input.

The drug product and indication proposed by the sponsor for non-prescription marketing (also known as over-the-counter or OTC) are identical to the approved prescription product. Plan B has previously been proven to be effective for emergency contraception, and has a well-documented safety profile. Therefore, the primary regulatory issue in considering the potential non-prescription use of this product is whether it can be used safely, effectively, and appropriately by women of child-bearing potential without need for a learned intermediary (e.g., counseling from a physician). In support of this application the sponsor submitted a label comprehension study and an actual use study, both of which have been extensively reviewed by the staff in the two divisions. In my opinion, these studies provide adequate evidence that women of childbearing potential can use Plan B safely, effectively, and appropriately for emergency contraception in the non-prescription setting. The data submitted by the sponsor in support of non-prescription use of Plan B are fully consistent with the Agency's usual standards for meeting the criteria for determining that a product is appropriate for such use. This conclusion is supported by the fact that both divisions and offices responsible for the review of this application have recommended approval and the fact that the joint Advisory Committee voted 23 to 4 in favor of recommending that Plan B be switched to non-prescription status.

Other senior officials within the Agency, including the former Commissioner **[Text Redacted]** and the Acting Center Director **[Text Redacted]**, have expressed concerns about the potential for unsafe, ineffective, or inappropriate use of Plan B by adolescents if it were to be made available without a prescription. These concerns appear to have been based primarily on the limited number of adolescent women included in the sponsor's label comprehension and actual use studies. While it is true that the number of adolescents enrolled in the sponsor's studies was relatively small, these studies did not exclude adolescent women from enrollment and were conducted in settings that would be expected to capture a representative population of women who currently seek emergency contraception. Therefore, it is likely that the percentage of patients enrolled in these studies is an accurate reflection of the potential users of Plan B in an OTC setting. Furthermore, the data from these studies do not suggest that adolescent women are significantly different from older women in their comprehension of the labeling or appropriate use of the product in the OTC setting, and for some analyses the adolescent women actually performed better than older women. I, therefore, believe that the data from the studies submitted by the sponsor are sufficient and adequate on which to base a regulatory decision on whether Plan B can be used safely, effectively, and appropriately by women of childbearing potential,



regardless of age, in the OTC setting. The Agency has not heretofore distinguished the safety and efficacy of Plan B and other forms of hormonal contraception among different ages of women of childbearing potential and I am not aware of any compelling scientific reason for such a distinction in this case. I would also note that the Agency has a long history of extrapolating findings from clinical trials in older patients to adolescents in both prescription and non-prescription approvals, and this practice was recently incorporated into the Pediatric Research and Equity Act (PREA).

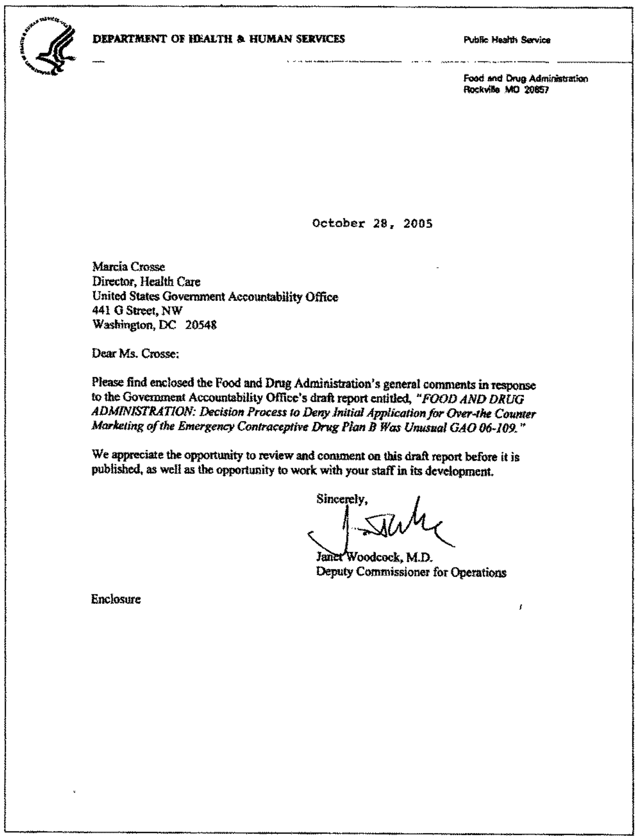
As detailed in the reviews prepared by **[Text redacted]**, in addition to the studies submitted by the sponsor there exists a substantial body of data from recently completed published and unpublished studies on emergency contraception that have enrolled a substantial number of adolescent women. While none of the studies directly mimic the OTC setting for access to Plan B, I believe that these data are relevant and help to address whether adolescents can use Plan B in the OTC setting. Taken together, these additional studies do not support a concern that adolescent women are less able to understand the label directions or less likely to appropriately use the product than older women. Further, these studies found that increased access for adolescents to emergency contraception did not result in inappropriate use of Plan B as a routine form of contraception, an increase in the number of sexual partners, an increase in the frequency of unprotected intercourse, or an increase in the frequency of sexually transmitted diseases.

In summary, I concur with the recommendations from the review divisions and offices that the sponsor has provided adequate data to demonstrate that Plan B can be safely, effectively, and appropriately used by women of childbearing potential for the indication of emergency contraception without a prescription. I, therefore, recommend that this application be approved to permit availability of Plan B without a prescription and without restrictions regarding the availability of the product to adolescent women.

I am sensitive to and respect the concerns that some may have regarding non-prescription access to Plan B by adolescents. Products that are indicated for uses related to sexual activity in adolescents raise concerns for some people that go beyond a finding based on clinical trial data that the product is safe and effective for its intended use in adolescents. These concerns are derived from individual views and attitudes about the morality of adolescent sexual behavior and also overlap with concerns about the role for parents and health care professionals in decisions about contraceptive use in adolescents. While acknowledging these concerns, I believe that the available data clearly support a conclusion that Plan B meets the statutory and regulatory requirements for availability without a prescription for all age groups. Such a conclusion is consistent with how the Agency has made determinations for other OTC products, including other forms of contraception available without a prescription. Further, I believe that greater access to this drug will have a significant positive impact on the public health by reducing the number of unplanned pregnancies and the number of abortions. While OTC access to Plan B for adolescents may be controversial from a societal perspective, I cannot think of any age group where the benefit of preventing unplanned pregnancies and abortion is more important and more compelling.

The sponsor is aware of the societal issues related to OTC access for Plan B, particularly to adolescents. They initially proposed a voluntary marketing plan called CARE (Convenient Access Responsible Education), which was designed to increase awareness of appropriate use of Plan B through education while increasing availability through OTC access. The joint Advisory Committee voted 22 to 5 (with one abstention) that this program was adequate for introduction of Plan B into the OTC setting. **[Remaining Text Redacted]**

Appendix VI: Comments from the Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

October 28, 2005

Marcia Crosse
Director, Health Care
United States Government Accountability Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Crosse:

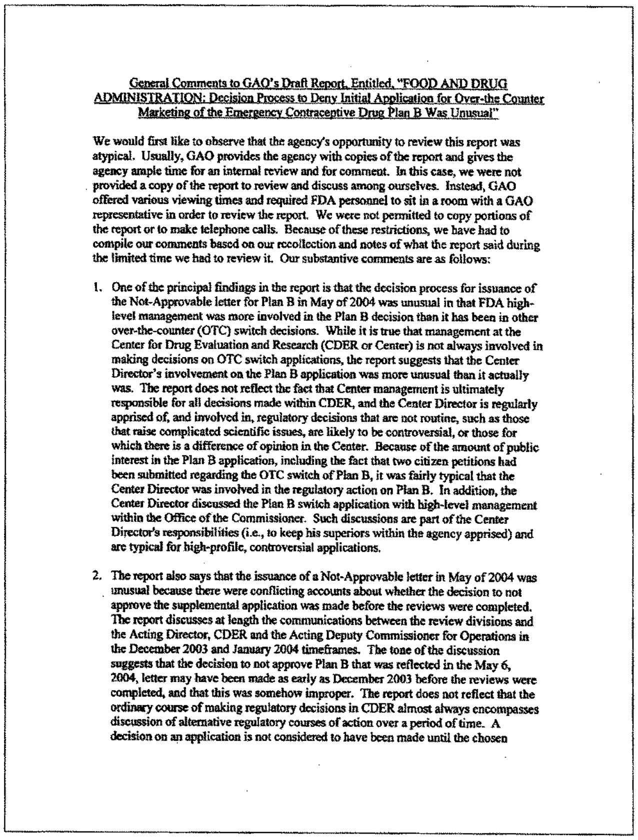
Please find enclosed the Food and Drug Administration's general comments in response to the Government Accountability Office's draft report entitled, *"FOOD AND DRUG ADMINISTRATION: Decision Process to Deny Initial Application for Over-the Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual GAO 06-109."*

We appreciate the opportunity to review and comment on this draft report before it is published, as well as the opportunity to work with your staff in its development.

Sincerely,

Janet Woodcock, M.D.
Deputy Commissioner for Operations

Enclosure



General Comments to GAO's Draft Report, Entitled, "FOOD AND DRUG ADMINISTRATION: Decision Process to Deny Initial Application for Over-the Counter Marketing of the Emergency Contraceptive Drug Plan B Was Unusual"

We would first like to observe that the agency's opportunity to review this report was atypical. Usually, GAO provides the agency with copies of the report and gives the agency ample time for an internal review and for comment. In this case, we were not provided a copy of the report to review and discuss among ourselves. Instead, GAO offered various viewing times and required FDA personnel to sit in a room with a GAO representative in order to review the report. We were not permitted to copy portions of the report or to make telephone calls. Because of these restrictions, we have had to compile our comments based on our recollection and notes of what the report said during the limited time we had to review it. Our substantive comments are as follows:

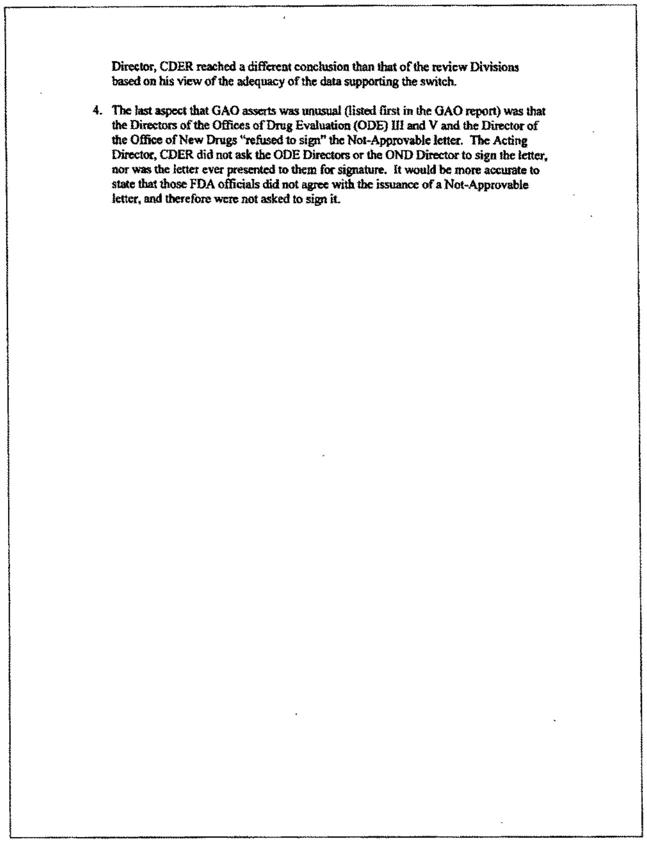
1. One of the principal findings in the report is that the decision process for issuance of the Not-Approvable letter for Plan B in May of 2004 was unusual in that FDA high-level management was more involved in the Plan B decision than it has been in other over-the-counter (OTC) switch decisions. While it is true that management at the Center for Drug Evaluation and Research (CDER or Center) is not always involved in making decisions on OTC switch applications, the report suggests that the Center Director's involvement on the Plan B application was more unusual than it actually was. The report does not reflect the fact that Center management is ultimately responsible for all decisions made within CDER, and the Center Director is regularly apprised of, and involved in, regulatory decisions that are not routine, such as those that raise complicated scientific issues, are likely to be controversial, or those for which there is a difference of opinion in the Center. Because of the amount of public interest in the Plan B application, including the fact that two citizen petitions had been submitted regarding the OTC switch of Plan B, it was fairly typical that the Center Director was involved in the regulatory action on Plan B. In addition, the Center Director discussed the Plan B switch application with high-level management within the Office of the Commissioner. Such discussions are part of the Center Director's responsibilities (i.e., to keep his superiors within the agency apprised) and are typical for high-profile, controversial applications.

2. The report also says that the issuance of a Not-Approvable letter in May of 2004 was unusual because there were conflicting accounts about whether the decision to not approve the supplemental application was made before the reviews were completed. The report discusses at length the communications between the review divisions and the Acting Director, CDER and the Acting Deputy Commissioner for Operations in the December 2003 and January 2004 timeframes. The tone of the discussion suggests that the decision to not approve Plan B that was reflected in the May 6, 2004, letter may have been made as early as December 2003 before the reviews were completed, and that this was somehow improper. The report does not reflect that the ordinary course of making regulatory decisions in CDER almost always encompasses discussion of alternative regulatory courses of action over a period of time. A decision on an application is not considered to have been made until the chosen

alternative is documented in an action letter, with supporting rationale. In the first cycle review of Plan B, regulatory alternatives were discussed as the original user fee performance goal date of February 20, 2004, approached. It was entirely normal for the Acting Center Director and others to convey to the review divisions their concerns regarding the application so the division could determine what communications with the applicant were appropriate as the goal date approached. It is inaccurate, however, to claim that a decision to issue a Not-Approvable letter was made several months before the action letter was issued. As the report itself indicates, as late as May 2, 2004, the Acting Director, CDER consulted with the Office of Pediatrics seeking more data on cognitive development in adolescents. The information received provided support for the conclusions reflected in the letter issued on May 6, 2004, documenting the action on the first review cycle of the application.

3. The third aspect of the action on Plan B that GAO found was "unusual" was that the rationale for the decision was "novel" and did not follow traditional practices, referring to the consideration of behavioral issues such as decreased use of condoms and increased risk of sexually transmitted diseases (STDs). This conclusion reflects a fundamental misunderstanding of the issues normally considered in OTC switch applications and the Acting Director's rationale supporting his action on the first cycle review of the Plan B supplemental application. First, all OTC switch applications require consideration of "behavioral" issues, including whether the disease or condition can be self-diagnosed and whether the drug can be used safely and effectively under actual conditions of use. Most switch applications are accompanied by actual use and label comprehension studies that examine such "behavioral" issues. In addition, the "behavioral" issues with regard to this application are directly related to safe use of the product. For example, if a woman chose not to use condoms and to rely on Plan B as her only form of contraception, she may be exposing herself to risks related to acquiring STDs, and if she relies on Plan B as her routine form of birth control, she would be exposing herself to the risks of regular oral contraceptives (which are only available Rx).

In the case of Plan B, the behaviors that were appropriate for consideration included sexual behaviors such as condom use and increased risk of STDs. Furthermore, the report suggests that the Acting Director, CDER alone identified these behavioral issues as concerns in his review. In fact, the Acting Director, CDER was not the source of these issues in the review of the Plan B supplemental application. Regarding the studies that were submitted by Barr and reviewed by the Divisions, the actual use study included specific questions about condom use and the label comprehension study included data from questions that assessed women's understanding that Plan B does not protect against STDs. The Acting Director, CDER reviewing the data in the application concluded that the data on actual use and label comprehension were inadequate to allow a conclusion that Plan B could be used safely and effectively in women under 16 because women in that age group were inadequately represented in the actual use and label comprehension studies. Rather than introducing a "novel" approach to this OTC switch application, the Acting



Director, CDER reached a different conclusion than that of the review Divisions based on his view of the adequacy of the data supporting the switch.

4. The last aspect that GAO asserts was unusual (listed first in the GAO report) was that the Directors of the Offices of Drug Evaluation (ODE) III and V and the Director of the Office of New Drugs "refused to sign" the Not-Approvable letter. The Acting Director, CDER did not ask the ODE Directors or the OND Director to sign the letter, nor was the letter ever presented to them for signature. It would be more accurate to state that those FDA officials did not agree with the issuance of a Not-Approvable letter, and therefore were not asked to sign it.

Appendix VII: GAO Contact and Staff Acknowledgments

GAO Contact	Marcia Crosse, (202) 512-7119 or crossem@gao.gov
Acknowledgments	In addition to the contact named above, Martin T. Gahart, Assistant Director; Cathleen Hamann; Julian Klazkin; Gay Hee Lee; and Deborah J. Miller made key contributions to this report.

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Attachment 5

Women's Health and the FDA

Susan F. Wood, Ph.D.

> Science commits suicide when it adopts a creed.
> — Thomas Henry Huxley[1]

On August 31, 2005, I resigned my post of assistant commissioner for women's health and director of the Office of Women's Health at the Food and Drug Administration (FDA). The agency leadership had chosen to delay indefinitely a decision about switching emergency contraception to nonprescription status. I believed that in doing so, they were disregarding the scientific and clinical evidence and the established review process and were taking an action that harms women's health by denying them appropriate access to a product that can reduce the rate of unplanned pregnancies and the need for abortions.

Both the relevant advisory committees and the professional review staff at the FDA's Center for Drug Evaluation and Research had strongly recommended that nonprescription status be granted to Plan B emergency contraception (levonorgestrel), given its safety and the need for timely access for optimal efficacy. The FDA had rejected the status change in 2004 on the basis of the stated concern that there were inadequate data showing comprehension and proper use by young teens, and it proposed making the product available over the counter only to women over a certain age; it has now delayed a decision, however, so that the difficulties raised by its own unprecedented proposal may be assessed.[2]

These actions should be examined in the broader context of the FDA's policies and programs for women's health. Women's health issues have been deeply entwined with the history of the agency. Congress's granting of the legal authority to the FDA to ensure that products are safe and effective was often driven by tragedies associated with women's health — often reproductive health, in particular. In 1962, when the Kefauver–Harris Amendments were added to the Food, Drug, and Cosmetic Act in response to the thalidomide tragedy, for example, the FDA gained critical authority, including the mandate to ensure that drugs were effective before being marketed and to require that manufacturers report unexpected adverse events. Thalidomide was denied approval for use in the United States; the evidence of its teratogenicity also led to the establishment, in 1977, of FDA guidelines calling for the exclusion of women of childbearing potential from phase 1 and early phase 2 studies — a policy that was not reversed until 1993.

In 1976, after the Dalkon Shield intrauterine device injured many women, Congress passed the Medical Device Amendments, strengthening the FDA's ability to regulate medical devices. In 1992, the FDA was given the responsibility of setting standards for and inspecting mammography facilities.

The agency's growing role in providing information has also been tied to women's health issues. In 1970, the FDA developed its first package insert for patients in response to calls from women's health advocates and the public for more consumer information about oral contraceptives. Such package inserts are now an important way of getting patients information on a wide variety of medicines. The discovery of a link between toxic shock syndrome and tampon use led to the provision of relevant information in tampon packaging. Recently, in response to new data, Congress called on the FDA to be the source of unbiased information about the risks and benefits of hormone therapy in menopause.

But women's health has meant more at the FDA than just reproductive health or women-specific health concerns. The key focus since 1993 on including women in all phases of clinical studies and evaluating the resultant data for differences according to sex and other demographic variables has affected all the products that come before the FDA — ensuring that studies explore the potential for sex differences in safety and efficacy and that data are collected rigorously enough to permit such evaluation. This issue was the primary reason for the formation, in 1994, of the FDA's Office of Women's Health. Current research and outreach activities of this office focus on coronary heart disease in women;

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other programs have targeted diabetes, pharmacokinetic and pharmacodynamic studies of medications used during pregnancy, and safe medication use. The office has also funded data-mining analyses of adverse drug events, as well as the development of systems for tracking the demographic characteristics of study subjects and analyzing data for significant sex differences.

The Office of Women's Health, which is part of the Commissioner's Office, is not in the usual decision-making chain for the approval of products at the FDA. But its staff members are often called on by the review centers to provide consultation, serve on working groups, or provide a broad perspective on women's health, particularly when a product under review has a clear link to women's health needs. The common threads in all our work have been the development of policy and programs for the benefit of the public health and a reliance on sound science for decision making.

Scientists and others sometimes raise questions about whether the FDA's decisions are in fact being guided by the available data, and vigorous and healthy debate over an agency decision is not unusual. Recent debates have focused on concerns about product safety and the structure of decision making with regard to safety labeling, and the Office of Women's Health played an appropriate role in these debates, as we did in the early discussions about Plan B.

The FDA holds dear its sometimes controversial prerogative to make decisions independent of its advisory committees, and there have been cases in which not accepting an advisory committee's recommendations has resulted in good decisions. But recommendations of an advisory committee that are strongly supported by the FDA's review staff have rarely, if ever, been overturned at the highest level of the agency, as they were both in the decision to reject nonprescription status for Plan B and in the most recent decision to delay through rule making. The first of these decisions, including the suggestion of possible dual status, overturned the recommendations of all the lower review levels in the Center for Drug Evaluation and Research. I disagreed with that 2004 decision, because such dual status has never been required for other over-the-counter products sold to adolescents and because the proposal was not based on concerns about safety or efficacy. Yet I and other staff members remained hopeful that this was indeed a path toward some form of approval.

But on August 26, 2005, the process appeared to have gone off track. The unusual decision to seek public comment and to begin the probable development of a new regulation to permit and govern such dual status — that is, to launch a rule-making process — came as a surprise to most of the agency. None of the senior members of the professional and scientific staff who would normally have participated in making a decision about nonprescription status for Plan B (all of whom had recommended approval) seemed to be aware of what the decision was going to be until shortly before it was announced. The staff members I spoke with indicated that they had not recommended this process, which can take years, as a needed step. The decision, which left women of all ages without appropriate and timely access to emergency contraception, was a clear rejection of recommendations that had been based on extensive review and evaluation of the pertinent data.

Recently, the commissioner of the FDA, Dr. Lester Crawford, stepped down; this will be the first test of whether a new commissioner will be able to ensure that science is the driving force in the agency. If the FDA is to continue to fulfill its important role in public health, both in the United States and internationally, its professional scientific and clinical staff must maintain its independence and thus its scientific credibility. In compromising these values and ignoring the expertise within the agency, the FDA's leadership has compromised the health of women and families. As a scientist, as a career FDA employee, and as the director of the Office of Women's Health, whose mission is to be the champion for women's health at the FDA, I could not sanction this action by remaining at the agency.

An interview with Dr. Wood can be heard at www.nejm.org.

Dr. Wood was the assistant commissioner for women's health and director of the Office of Women's Health at the Food and Drug Administration, Rockville, Md., from November 2000 to August 2005. She is an adjunct associate professor at the School of Public Affairs at American University, Washington, D.C.

1. Reflection #71. In: Aphorisms and reflections — from the works of T.H. Huxley, selected by Henrietta A. Huxley. London: MacMillan, 1907.
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Attachment 6

The Washington Post

When Politics Defeats Science

By Susan F. Wood
Wednesday, March 1, 2006; A17

Since my resignation six months ago as assistant commissioner of women's health at the Food and Drug Administration, I have been traveling around the country meeting with men and women, fellow scientists and health care professionals. I have shared my concerns that our federal health agencies seem increasingly unable to operate independently and that this lack of independence compromises their mission of promoting public health and welfare.

At every stop I am reminded that whether it is the environment, energy policy, science education or public health, the American public expects our government to make the best decisions based on the best available evidence.

Yet, at a recent hearing of the House Appropriations subcommittee on labor, health and human services, we saw once again that this is not happening. Reps. Sam Farr (D-Calif.) and Rosa DeLauro (D-Conn.) questioned FDA acting commissioner Andrew C. von Eschenbach about the delay in approving the application to make Plan B emergency contraception available over the counter to women 17 and older. Von Eschenbach responded that the agency was carefully reviewing the thousands of comments received in response to last-minute concerns raised about the feasibility of making the same product available over the counter for most women but keeping it on prescription for young teens. This exchange confirmed my suspicion that, like his predecessor, von Eschenbach is unable or unwilling to let the science and the scientists guide FDA policy and decisions, and that the real answer as to whether the FDA will allow Plan B over the counter for those 17 and older is no.

Time and again in my travels I am asked, "What happened to derail Plan B?" I have to answer honestly that I don't know. The manufacturer agreed to take the "controversial" issue of young teens' access to emergency contraception off the table in 2004; now we are talking only about adult access to safe and effective contraception. Over 98 percent of adult women have used some form of contraception. So what is the objection?

Perhaps it is that posed by a small but vocal political minority that insists on labeling emergency contraception as abortion, or at least confusing the two. One of the main questions I hear is, "Does this pill cause an abortion?" In fact, the only connection this pill has with abortion is that it has the potential to prevent the need for one. Emergency contraceptive pills work exactly the same way as other birth control pills, and they do not interfere with or harm an existing pregnancy. Emergency contraception is simply a higher dose of daily birth control pills; it is not RU-486, the "abortion pill." Indeed, emergency contraception has been used as a method to prevent unintended pregnancies for decades by women who had physicians advise them on how many pills in their regular pill pack to take. So people who are comfortable with oral contraceptives as methods of contraception should be just as comfortable with emergency contraception.

Having spent 15 years working for the federal government, nearly five of which were at the FDA, I care deeply about what's happening in the federal agencies, particularly our health agencies. Nearly 25 cents of every consumer dollar is spent on products regulated by the Food and Drug Administration. We count on the FDA for the safety and effectiveness of our medicines, vaccines and medical devices, and for the safety of the blood and food supply. The American public does not want to -- nor should it -- have to think twice about the quality and reliability of information it is getting from the FDA. Its reputation as the international gold standard for regulatory agencies, and as a body that sets the bar very high when it comes to scientific evidence and integrity, is being put at risk over adult access to contraception. Why would the administration risk such a reputation over this?

Von Eschenbach could demonstrate his commitment to the FDA's independence and scientific integrity and help restore staff morale and waning public credibility by stopping the rulemaking process and approving access to Plan B for women 17 and older. Instead, he continues to hide behind a wasteful and pointless bureaucratic process. Congress needs to step in and restore the FDA's independence and its ability to make decisions based on the evidence.

It's been nearly three years since the first application came in to make Plan B emergency contraception available over the counter, so that women, including rape victims, could have a second chance to prevent an unintended pregnancy and the need for an abortion. How many chances have we missed? I still can't explain what is going on here, and why women 17 and older are still denied this product in a timely way. When did adult access to contraception become controversial? And why have we allowed it to happen?

The writer is a former assistant commissioner of the Food and Drug Administration and is a senior policy adviser to the Reproductive Health Technologies Project.

Attachment 7

Reproductive Health Technologies Project

Mission Statement

The mission of the Reproductive Health Technologies Project is to advance the ability of every woman of any age to achieve full reproductive freedom with access to the safest, most effective, appropriate and acceptable technologies for ensuring her own health and controlling her fertility. To fulfill this mission, we seek to build consensus in support of an education, research and advocacy agenda for reproductive health and reproductive freedom. We seek consensus through a process of dialogue among diverse communities about technological developments and their global implications.

Guiding Principles

- We strive to identify and eliminate barriers and ensure access to reproductive health information and technologies.
- We view technology not as an end in itself, but as an essential component for all women and men, including those who are underserved and historically have been excluded, to control their own health and fertility.
- We believe that each technology requires careful analysis of its safety, effectiveness, acceptability, appropriateness and ethical aspects, recognizing that all of these may vary from person to person and community to community.

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Washington, DC 20036

Site design: OmniStudio

Attachment 8

NATIONAL WOMEN'S HEALTH NETWORK
Gynuity HEALTH PROJECTS
Reproductive Health Technologies Project
Ipas
naf NATIONAL ABORTION FEDERATION

May 11, 2006

To Members of the Committee on Emerging Clostridial Disease,

As representatives of Gynuity Health Projects, Ipas, the National Abortion Federation, the National Women's Health Network, and the Reproductive Health Technologies Project, we applaud the Centers for Disease Control, the Food and Drug Administration, and the National Institute of Allergy and Infectious Diseases for holding a joint scientific gathering. We are hopeful that the expertise reflected in the room and among many of the presenters will help all of us develop a better understanding of a challenging public health problem.

Like you, women's health experts and advocates across the country are concerned by the deaths of four women from *Clostridium sordellii* following medical abortion. According to reports from Centers for Disease Control, we understand this is part of a larger pattern of fatal infection among obstetric and gynecologic patients, many of whom were pregnant, but at least one of whom was not, and that this in turn may be part of a larger emerging pattern of clostridial infection.

A number of women's reproductive health organizations and experts have come together to share knowledge, expertise and resources in an effort to better inform the prevention and treatment care which may be offered to obstetric and gynecologic patients, particularly those who are seeking to end an early pregnancy with a medical abortion procedure. We are hopeful that the technical expertise and resources represented by the convening agencies will be used to investigate the underlying pathology of these infections and evaluate different options for care.

We want to learn from your discussions and also raise several questions we hope you will consider as you develop a research agenda.

- Are the four confirmed deaths from *C. sordellii* following medical abortion related to an alternate, unusual, or mutated form of the organism?
- Are there examples of infection among obstetric and gynecologic patients who have survived this infection? If yes, what sets these cases apart? Do these cases provide any insight for treatment options or guidelines?
- A pressing question in the context of abortion care is the role of prophylactic treatment with antibiotics. To date, the FDA has cautioned against that approach, noting that with limited data, it is not clear that the benefits outweigh the risks. We urge the collection of public health experts to prioritize a research agenda that will help health care providers better evaluate treatment options for their patients.
- Is there a potential anti-toxin that could be developed as a reasonable approach to saving lives from this infection, akin to the antivenin treatments available for snakebite victims?

The signatories to this letter also want to express our commitment and willingness to work with public health professionals at a national and local level to better determine options for prevention and treatment in emerging clostridial infection, particularly as it relates to obstetric and gynecologic care. We want to thank you for your leadership on this issue and for the opportunity to share our concerns.

Sincerely,

Beverly Winikoff, MD, MPH
President
Gynuity Health Projects
212.448.1230

Laura Castleman, MD, MPH
Medical Director
Ipas
248.390.6272

Vicki Saporta
President and CEO
National Abortion Federation
202-667-5881 ext. 219

Amy Allina
Program and Policy Director
National Women's Health Network
202.347.1140

Kirsten Moore
President and CEO
Reproductive Health Technologies Project
202.215.4019

Statement of Vicki Saporta, President and CEO
National Abortion Federation
Submitted to the House Subcommittee on
Criminal Justice, Drug Policy, and Human Resources
May 17, 2006

The National Abortion Federation (NAF) is the professional association of abortion providers in the United States and Canada. NAF's mission is to ensure safe, legal, and accessible abortion care to promote health and justice for women. NAF's members include physicians, advanced practice clinicians, nurses, counselors, administrators, and other medical professionals at more than 400 facilities. NAF members are recognized experts in abortion care and include non-profit and private clinics, women's health centers, Planned Parenthood facilities, hospitals, and private physicians' offices, as well as nationally and internationally recognized researchers, clinicians, and educators at major universities and teaching hospitals. Together, they care for more than half the women who choose abortion each year in the United States.

NAF welcomes the opportunity to submit comments to the House Subcommittee on Criminal Justice, Drug Policy, and Human Resources. NAF has extensive experience with mifepristone (also known as RU-486 and marketed in the United States under the name Mifeprex). We developed education and training resources for health care providers, patient education materials, and information for the general public to coincide with the approval of mifepristone in 2000. Since its approval, NAF has continued to educate and train providers in its use, educate women about the option, and has carefully monitored developments concerning mifepristone's safety and efficacy.

Mifepristone has a long and well-established record of safety. First licensed in France and China in 1988, it has since been approved in 36 countries. Millions of women world-wide have safely used mifepristone, including approximately 600,000 women in the United States. Mifepristone in conjunction with misoprostol is a safe and effective regimen for early medical abortion. Major complications associated with its use are rare. The FDA approved mifepristone based on extensive medical and scientific evidence. Since its approval, however, opponents of abortion have attempted to restrict women's ability to access this safe and effective method for early abortion.

Numerous allegations have been made that the FDA "fast-tracked" their review of mifepristone. The FDA approved mifepristone following more than four years of review, contrasting with a median 15.6 month approval time for all other new molecular entities approved in that year. The approval of mifepristone was not accelerated, nor did mifepristone bypass the standard review process for new medications. For the approval of mifepristone, the FDA invoked a provision known as "Subpart H," which allows the FDA to establish a distribution system to assure safe use of certain drugs the agency has found to be effective. Subpart H was only invoked after the clinical trials had been concluded and an approvable letter had been issued. There has been a great deal of confusion over this provision as it has also been invoked for accelerated approvals in other contexts, such as with certain HIV and cancer treatments. The safety and efficacy of mifepristone, however, was thoroughly reviewed during regular clinical trials, which were not accelerated or abbreviated.

Since its approval by the FDA in 2000, there have been two revisions to the labeling for mifepristone, most recently in July 2005, in order to incorporate expanded safety information including precautions and warning signs for infection, ectopic pregnancy, and excessive bleeding. Corresponding patient education materials from the manufacturer have been amended to reflect these changes, and have been incorporated into NAF's educational materials.

Six deaths in the United States have been reported in women following the use of mifepristone/misoprostol. One death reported following the use of mifepristone and misoprostol was due to a ruptured ectopic pregnancy. Ectopic pregnancy is a pre-existing condition not caused by the use of mifepristone and misoprostol, and these medications are not an effective treatment for ectopic pregnancy. Ectopic pregnancies develop outside of the uterus, usually in the fallopian tube, occur in 2% of all pregnancies, and are the most common cause of death in the first trimester of pregnancy. As an ectopic pregnancy grows, it damages the tube causing it to rupture (burst) and bleed.

Reports of fatal infection in women using mifepristone/misoprostol are very rare. Four deaths have been attributed to sepsis following *Clostridium sordellii* infection and one death reportedly linked to another clostridial organism, *Clostridium perfringens*, is currently under investigation. *Clostridium sordellii* is a species of bacteria that in very rare cases causes toxic shock that is rapidly fatal. Four of the confirmed cases of *Clostridium sordellii* have occurred in California. Very little is known about how or why *Clostridium sordellii* becomes lethal. *Clostridium sordellii* has also been identified as a cause of death following childbirth, surgery, and trauma.

The public health community is seriously studying the rise in clostridial disease. A second strain of bacteria, *Clostridium difficile*, has been responsible for hundreds of deaths in the United States. On May 11, the Centers for Disease Control, the Food and Drug Administration, and the National Institute of Allergy and Infectious Diseases held a scientific meeting on emerging clostridial disease in the United States. As advocates for women's health, we are deeply concerned about the deaths of four women from *Clostridium sordellii* following medical abortion and the larger pattern of fatal infection among obstetric and gynecologic patients.

NAF will work with public health officials as they develop resources and guidelines for preventing and treating clostridium infections. In reviewing the four cases following use of mifepristone, the FDA has not found a causal relationship between the *Clostridium sordellii* infections and either of the two drugs used in medical abortion, mifepristone and misoprostol, or their method of administration. The FDA tested batches of mifepristone and misoprostol and confirmed that they were not contaminated. Notably, clostridium bacteria are found in about 4-18% of healthy women and one estimate is that 1% of those women carry the *sordellii* species. Scientists do not yet know what causes deadly toxins to be produced.

Based on the medical and scientific evidence, mifepristone is a safe and effective way to terminate an early pregnancy. Mifepristone has been well accepted by patients and providers; approximately 600,000 American women have chosen mifepristone to end their pregnancies. Women choose mifepristone over surgical abortion for a variety of reasons. Many women choose medical abortion because it is noninvasive and may seem more natural and more private. Also, some women have conditions that may make medical abortion preferable such as vaginal scarring, large uterine fibroids, certain abnormalities of the uterus or cervix, or obesity.

As an organization representing health care providers and the women for whom they care, NAF is committed to ensuring the highest standards of medical care. We fully support scientific inquiry into the recent cases of *Clostridium sordellii* and *Clostridium difficile*. Such investigations, however, should be based on medical and scientific evidence, not political agendas. Women deserve the best available health care options, including access to mifepristone, a method proven to be safe and effective for ending an early pregnancy. The withdrawal of mifepristone from the market or the imposition of medically unjustified restrictions on its use without sound scientific evidence would set a dangerous precedent for the regulation of health care in the United States. NAF urges members of the Subcommittee to consider science rather than politics when debating this very important public health issue.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

JUL 20 [illegible]

Mr. Walter M. Weber
Senior Litigation Counsel
American Center for Law & Justice
201 Maryland Avenue, N.E.
Washington, D.C. 20002

Dear Mr. Weber:

We appreciate your interest in the Centers for Disease Control and Prevention's (CDC) efforts to collect and publish maternal mortality statistics (including those related to abortion). CDC makes every effort to identify all such deaths and to present maternal mortality statistics using established scientific methods.

The maternal mortality rate is computed as all maternal deaths per 100,000 live births. In contrast, the measure used for abortions is a case-fatality rate which is computed per 100,000 legal abortions. These measures are conceptually different and are used by CDC for different public health purposes.

CDC calculates the maternal mortality rate per 100,000 live births for the following reasons:

1. To maintain comparability in long term trends for the United States. Estimates of the number of pregnancies (including live births, miscarriages or stillbirths, and induced abortions) in the United States have been published only since the 1970s.
2. The live birth component of the pregnancy estimates is highly reliable. Virtually all births are counted in every year. Estimates of all abortions are based on CDC's abortion surveillance system, which relies on state abortion reporting systems. Estimates of stillbirths, ectopic pregnancies, and miscarriages are based on survey data and are subject to significant sampling error, particularly for smaller population subgroups. Estimates of stillbirths and miscarriages are based on pregnancy history data from the National Survey of Family Growth (NSFG). The NSFG is conducted periodically, every 5 to 7 years. The data are subject to sampling error, particularly for smaller population subgroups. For information on the estimation methodology, see www.cdc.gov/nchs/data/series/sr_21/sr21_056.pdf.
3. To maintain international comparability. Many other countries cannot adequately estimate the number of pregnancies, especially those in which abortion is illegal. Information on miscarriage and stillbirth also varies considerably in completeness. In the interest of international comparability, the World Health Organization has specified that the number of live births should be used for the denominator of the maternal mortality rate.

Adjusting the maternal mortality rate for gestational stage is not statistically feasible, because this requires data that are not currently completely available. The Pregnancy Mortality Surveillance System (PMSS) relies primarily on death certificates which do not typically provide this information. Gestational age may be available for some maternal deaths in cases where linkage with other records (e.g., birth certificates, fetal death reports) is possible. Information on gestational age for induced abortions is available in about 42 states or jurisdictions.

CDC recognizes that despite efforts to count all maternal deaths (including those abortion-related) in the United States, some remain uncounted. The death itself is reported but accurate information on the cause may not be provided. CDC estimates that maternal deaths in general are underreported by 30 to 150 percent (see www.cdc.gov/mmwr/preview/mmwrhtml/ss5202a1.htm). The nature of the surveillance systems make it difficult to obtain complete data. The PMSS compiles data from 50 states, the District of Columbia, and New York City. Abortion surveillance involves data from 47 states, District of Columbia, and New York City. These systems are voluntary (CDC does not provide remuneration for data) and rely primarily on death certificate data which may or may not provide information that indicates the death was maternal or abortion-related. In the case of deaths associated with induced abortion, CDC also uses searches of computerized print media databases (Lexis-Nexis) to identify additional cases.

At CDC we are very committed to improving data collection systems and providing the most accurate and reliable data on all aspects of maternal and infant health. I hope this information is helpful.

Sincerely,

Julie Louise Gerberding, M.D., M.P.H.
Director

April 30, 2004

Tommy G. Thompson
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Re: Abortion statistics and maternal health

Dear Secretary Thompson:

In the challenges to the federal partial birth abortion statute, as on many other occasions, the proponents of legalized abortion make the claim that abortion is safer for women than childbirth. There is very good reason to believe that this claim is false. However, a fair scientific examination of this claim is hindered by the way the Centers for Disease Control (CDC) maintains its relative maternal mortality statistics.

I am writing to urge your office to direct a reassessment of the pertinent statistical measures. In short, the HHS should see to it that the American public -- and in particular, women contemplating the choice between abortion and continuing pregnancy -- have a genuine basis for an honest and meaningful comparison of the relative risks. If, in the alternative, the CDC is unable to provide a basis for a true comparison, it should so state.

The CDC has in the past reported maternal mortality as the "[n]umber of maternal deaths per 100,000 live births." See, e.g., www.cdc.gov/epo/mmwr/preview/mmwrhtml/00054602.htm (Fig. 1, footnote *) (Maternal Mortality -- United States, 1982-1996). Abortion mortality, by contrast, is reported as the number of "[l]egal induced abortion-related deaths per 100,000 reported legal induced abortions." See, e.g., www.cdc.gov/mmwr/preview/mmwrhtml/ss5212a1.htm (Table 19, footnote *) (Abortion Surveillance -- United States, 2000).

Here are some of the concerns with these statistics:

1. Denominator too small for maternal mortality rate

Maternal mortality should reflect deaths per pregnancy, not deaths per live birth. Stillbirths and miscarriages are fairly common occurrences.[1] To count maternal deaths associated with miscarriages, for example, while not counting the pregnancies, improperly inflates the maternal mortality rate.[2]

2. No maternal mortality rate adjustment for gestational stage

The relative risk of aborting versus continuing a pregnancy should reflect the prospective risks only, and not risks associated with stages of pregnancy already passed. For example, ectopic pregnancies cause a significant percentage of maternal deaths, and indeed are the leading cause of deaths in the first trimester. See, e.g., www.cdc.gov/mmwr/preview/mmwrhtml/00035709.htm (Current Trends: Ectopic Pregnancy -- United States, 1990-92). Obviously, a woman entering her second trimester faces zero risk of a first-trimester death from ectopic pregnancy, yet the undifferentiated CDC maternal mortality rate incorporates those first-trimester deaths. An abortion cannot eliminate risks that have already passed; only prospective risks should enter into the comparison.

3. Underreporting of abortion-related deaths

A true statistical comparison of the risks of death from abortion versus continued pregnancy is impossible if the statistics are inaccurate. Thus, the apparently common failure to report abortion-related deaths, see www.afterabortion.org/PAR/V8/n2/abortiondeaths.html ("The Cover-Up: Why U.S. Abortion Mortality Statistics Are Meaningless"), underestimates the abortion mortality rate. The same problem would apply to any underreporting of other maternal deaths. (And, of course, abortion-related deaths must be excluded from the maternal mortality rate if any comparison is to be made. Counting abortion deaths as maternal deaths as well -- or instead -- stacks the deck against childbearing and in favor of abortion.)

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[1] See, e.g., www.cdc.gov/nchs/releases/00facts/trends.htm ("6 million-plus pregnancies in 1996 in the U.S. resulted in 3.9 million births, 1.3 million induced abortions and almost a million fetal deaths," i.e., "16 percent [ended] in a miscarriage or stillbirth").

[2] Of course, live births should be counted only once for each labor, regardless of whether the woman bears at one time a single child, twins, triplets, or a greater number.

4. Disregard of non-immediate deaths

Recent studies indicate that abortion is associated with an increased rate of short-term and long-term maternal death. See www.afterabortion.org/physica.html ("A list of Major Physical Sequelae Related to Abortion"). A fair comparison of abortion with continued childbearing, like a fair comparison of smoking with nonsmoking, would take into account all such statistically significant increased death risks.

* * *

Women choose or decline abortions for many different reasons, and the decision for many may represent a complex balance of multiple considerations. It is a grave disservice to withhold from women the information needed for a genuine comparison between abortion mortality and the risk of mortality from continuing the pregnancy. Such information may be decisive for many women. Moreover, abortion businesses, which have profit motives for women to choose abortion, cannot be relied upon to present the full picture. Indeed, such businesses may be using statistics -- despite the flaws described above -- to help sell abortion to trusting lay women. Cf. www.abortion.com/questions.html (claiming that "statistically, childbirth is far more dangerous than abortion").

I strongly urge you to direct the CDC to make all necessary adjustments to its preparation and presentation of statistical data to allow for an honest, unbiased comparison of the relative risks of abortion and continuing pregnancy.

Very truly yours,

Walter M. Weber
Senior Litigation Counsel

WMW:fd

cc: Timothy Goeglein
Terrell Halaska

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EARLY PREGNANCY TERMINATION WITH MIFEPRISTONE AND MISOPROSTOL IN THE UNITED STATES

IRVING M. SPITZ, M.D., D.SC., C. WAYNE BARDIN, M.D., LAURI BENTON, M.D., AND ANN ROBBINS, PH.D.

ABSTRACT

Background Mifepristone and a prostaglandin have been used successfully to terminate pregnancy in Europe and China. We report the results of a large U.S. study of mifepristone and misoprostol in women with pregnancies of up to nine weeks' duration.

Methods We administered 600 mg of mifepristone and then 400 μg of misoprostol two days later to 2121 women seeking termination of their pregnancies at 17 centers. The women were observed for four hours after the administration of misoprostol and returned on day 15 for final assessment.

Results Two thousand fifteen women completed the final assessment. Among them, pregnancy was terminated in 762 of the 827 women pregnant for $\leq$49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) ($P<0.001$). Termination occurred within 4 hours after the administration of misoprostol in 49 percent of the women and within 24 hours in 75 percent. Failures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of pregnancy. The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the $\leq$49-days group to 9 percent in the 57-to-63-days group ($P<0.001$). Abdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age. Two percent of the women in the $\leq$49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids ($P=0.008$).

Conclusions This mifepristone–misoprostol regimen is effective in terminating pregnancies, especially in women with pregnancies of 49 days' duration or less. (N Engl J Med 1998;338:1241-7.)

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THE antiprogestin mifepristone (RU 486) causes abortion by competitively blocking progesterone receptors.[1-3] For maximal effectiveness, a prostaglandin should be given 48 hours after mifepristone.[1,3,4] The rates of termination of pregnancies 49 days old or less are similar, ranging from 96 to 99 percent, whether mifepristone is used with gemeprost or misoprostol, both prostaglandin E_1 compounds.[1,3,5-7] Gemeprost is expensive, requires refrigeration, and is not widely available, but misoprostol is inexpensive, stable at room temperature, and obtainable in many countries, including the United States.

Many American women do not have access to abortion,[8] and in developing countries up to 200,000 women die annually of complications after illegal abortions.[9] The availability of medical abortion in the United States and elsewhere could lead to greater access to safer abortion services. We conducted a multicenter trial of mifepristone and misoprostol to determine whether this combination could be used to terminate pregnancies of up to 63 days' duration.

METHODS

Participating Centers

From September 1994 to September 1995, we enrolled 2121 women, each with a documented pregnancy of 63 days' duration or less, requesting termination of pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or known allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than 10 cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had in situ intrauterine devices, were breast-feed-

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From the Center for Biomedical Research, Population Council, 1230 York Ave., New York, NY 10021, where reprint requests should be addressed to Dr. Robbins.

The principal investigators and centers participating in the study are listed in the Appendix.

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ing, were receiving anticoagulation or long-term glucocorticoid therapy, had adnexal masses, had ectopic pregnancies, or had signs or symptoms suggesting they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. Among the 2121 women, 915 were enrolled at eight Planned Parenthood clinics, 538 at four university-hospital clinics, and 668 at five free-standing abortion clinics. The protocol was approved by the human investigational review board at each participating institution, and all the women gave informed consent.

Study Design

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography. On the basis of the investigator's final assessment of these three measures, the women were assigned to the following arbitrarily defined gestational-age groups: the ≤49-days group (859 women); the 50-to-56-days group (722); and the 57-to-63-days group (540).

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took 600 mg of mifepristone orally. At visit 2 (day 3), they took 400 μg of misoprostol orally unless a complete abortion had already occurred. After taking misoprostol, the women were monitored for four hours for adverse events, such as nausea, vomiting, diarrhea, and abdominal pain. These events were rated by the women and recorded as mild (felt but easily tolerated), moderate (uncomfortable enough to interfere with usual activity), or severe (incapacitating, preventing usual activity). Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 of the study as spotting (less than normal menstrual bleeding), normal (similar to normal menstrual bleeding), or heavy (more than normal menstrual flow). During this period, the women were also monitored for expulsion of the conceptus. At visit 3 (day 15), the treatment outcome was assessed.

Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure. The need for a surgical procedure (either vacuum aspiration or dilation and curettage) constituted a failure, and such a procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion. Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to follow up; 5 had continuing pregnancies when last seen at visit 2. The analyses of efficacy therefore included 2015 women.

Statistical Analysis

Statistical analysis was performed with the use of Statistical Analysis System software (SAS Institute, Cary, N.C.). One-way analysis of variance and Kruskal–Wallis tests were used to compare mean values in the gestational-age groups, and Pearson's chi-square tests were used to compare the distributions of categorical variables. Fisher's exact test was used to compare rates in the gestational-age groups. Stepwise logistic-regression analysis was used to evaluate the relation between success or failure and various base-line patient characteristics; the significance level required for a variable to stay in the model was 0.10. All statistical tests were two-tailed.

RESULTS

There were 859 women in the ≤49-days group, 722 in the 50-to-56-days group, and 540 in the 57-to-63-days group. The three groups were similar with respect to age (mean, 27 years; range, 18 to 45), gravidity, parity, number of spontaneous or previous elective abortions, and ethnic or racial distribution (white, 71 percent; black, 15 percent; Hispanic, 9 percent; Asian, 5 percent). Seventy-three percent of the women had had previous pregnancies, 51 percent elective abortions, and 15 percent spontaneous abortions.

Efficacy

Among the 2015 women who returned for the third visit, the rates of pregnancy termination were 92 percent in the ≤49-days group, 83 percent in the 50-to-56-days group, and 77 percent in the 57-to-63-days group ($P<0.001$) (Table 1). Of the 59 women who did not receive misoprostol, 56 had termination of their pregnancies after mifepristone alone. In the remaining three women, it subsequently became apparent that their pregnancies had not been terminated after mifepristone and they should have been given misoprostol; they later underwent surgical termination. The rate of termination after mifepristone alone also decreased significantly with increasing gestational age, from 5 percent to 0.8 percent (Table 1).

The rates of incomplete abortion were 8 percent in the 50-to-56-days group and 7 percent in the 57-to-63-days group, as compared with 5 percent in the ≤49-days group (Table 1). The failures for all other reasons were significantly higher in both the 50-to-56- and 57-to-63-days groups than in the ≤49-days group. The largest increase was in failures representing ongoing pregnancy, which rose from 1 percent in the ≤49-days group to 9 percent in the 57-to-63-days group. Ninety percent of the surgical terminations performed for medical reasons were for vaginal bleeding. A patient's request was the reason least often cited for surgical termination.

Although the study design called for analysis according to the three discrete gestational-age groups, there was in fact a steady decline in the frequency of termination of pregnancy with increasing duration of gestation (Fig. 1). Logistic-regression analysis indicated that the rates decreased with increasing gestational age, from more than 95 percent before day 40 to less than 90 percent after day 47 and to less than 80 percent after day 59. The only other factor that was related to outcome was the number of previous elective abortions (Fig. 1); the termination rates were higher for women with no previous abortions than for those with previous abortions. The differences in rates were less than 2 percent up to day 35, 2 to 3 percent from days 36 to 42, 3 to 4 percent from days 43 to 48, 4 to 6 percent from days 49 to 55, and 6 to 10 percent from days 56 to 63. The outcomes were unrelated to other base-line characteristics, including age, race, body weight, gravidity, and previous spontaneous abortions.

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TABLE 1. RESULTS OF MIFEPRISTONE AND MISOPROSTOL IN WOMEN SEEKING TERMINATION OF PREGNANCY.

OUTCOME	PREGNANT ≤49 DAYS (N=827)	PREGNANT 50 TO 56 DAYS (N=678)	PREGNANT 57 TO 63 DAYS (N=510)
	number (percent [95% confidence interval])		
Success	762 (92 [90–94])	563 (83 [80–86])*	395 (77 [74–81])*†
After mifepristone alone	40 (5)	12 (2)‡	4 (0.8)*
Failure (need for surgical intervention)			
Medical indication for intervention	13 (2)	26 (4)‡	21 (4)‡
Patient's request for intervention	5 (0.6)	13 (2)	
Incomplete abortion	39 (5)	51 (8)‡	12 (2)‡
Ongoing pregnancy	8 (1)	25 (4)*	36 (7) 46 (9)*§
Total	65 (8)	115 (17)*	115 (23)*†

*P<0.001 for the comparison with the ≤49-days group.

†P=0.02 for the comparison with the 50-to-56-days group.

‡0.001≤P<0.03 for the comparison with the ≤49-days group.

§P<0.001 for the comparison with the 50-to-56-days group.

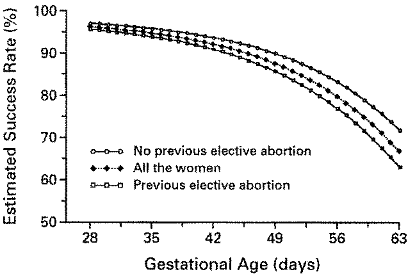

Figure 1. Logistic-Regression Analysis of the Predicted Probability of Successful Pregnancy Termination, According to the Duration of Pregnancy for All the Women and for the Women Who Had and Those Who Had Not Had Previous Elective Abortions.

Complete expulsion of the conceptus occurred before the administration of misoprostol in 76 women (4 percent). This group included the 56 women who received only mifepristone and an additional 20 women who received misoprostol because their expulsion status was considered uncertain at the beginning of visit 2. It was subsequently determined that these 20 women had had complete expulsions before they took misoprostol. During the four hours of observation after the administration of misoprostol, 49 percent of the women expelled the conceptus, and during the fifth hour an additional 11 percent expelled the conceptus. By 24 hours after misoprostol administration, 75 percent of the women had expelled the conceptus (Fig. 2).

Vaginal Bleeding

Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated medically. The median duration of bleeding or spotting was 13 days in the ≤49-days group and 15 days in the other two groups (P<0.001). The proportions of women who reported heavy bleeding did not differ significantly in the three groups, were highest on day 3, and then decreased steadily. By day 15, 77 percent of all reported bleeding was considered spotting (Fig. 3). Nine percent of the women reported some type of bleeding after 30 days, and 1 percent after 60 days.

Excessive bleeding necessitated blood transfusions in four women and accounted for 25 of 27 hospitalizations (including emergency-room visits), 56 of 59 surgical interventions, and 22 of 49 administrations of intravenous fluid. Hospitalizations, surgical interventions, and intravenous-fluid administration were reported for 2 percent of the women in the ≤49-days group and for 4 percent of those in each of the other groups (P=0.008). Bleeding was managed by the administration of uterotonic agents, such as oxytocin, methylergonovine, or vasopressin, in 41 women (5 percent) in the ≤49-days group, 50 (7 percent) in the 50-to-56-days group, and 55 (10 percent) in the 57-to-63-days group (P<0.001).

Other Adverse Events

Almost all the women (99 percent) reported at least one adverse event during the study period (Ta-

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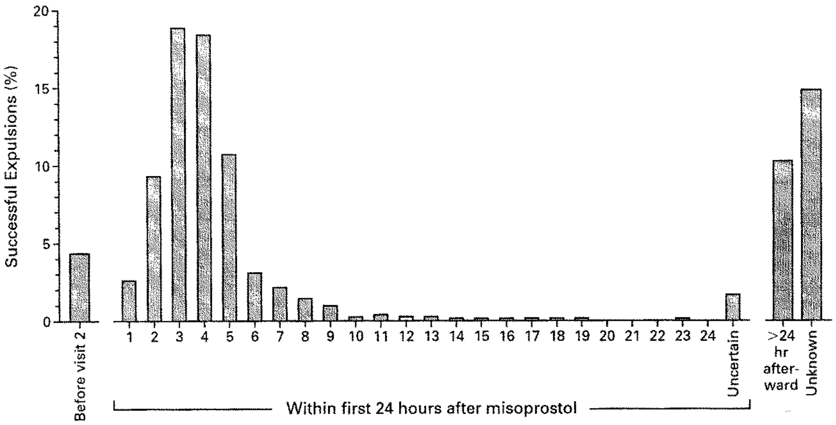

Figure 2. Times of Expulsion of the Conceptuses in 1720 Women with Successful Termination of Their Pregnancies.

The women received mifepristone at visit 1 and misoprostol two days later (visit 2). "Uncertain" indicates that expulsion occurred within the first 24 hours after misoprostol was given, but the exact time was not known. "Unknown" indicates that expulsion occurred more than 24 hours after misoprostol was given, but the exact time was not known.

ble 2). Nearly all had abdominal pain; its overall incidence did not differ among the three groups. However, 53 percent of the women in the 50-to-56-days group and 54 percent in the 57-to-63-days group had abdominal pain reported as severe, as compared with 43 percent in the ≤49-days group ($P<0.001$). Sixty-eight percent of the women received at least one medication for abdominal pain (usually acetaminophen), and 29 percent also received opiates (usually acetaminophen with hydrocodone or codeine). The women in the 50-to-56- and 57-to-63-days groups received significantly more analgesia and opiates than the women in the ≤49-days group ($P<0.001$). Abdominal pain resulted in one hospitalization and was the reason for two medically indicated surgical interventions.

As compared with the ≤49-days group, the 50-to-56- and 57-to-63-days groups had significantly more nausea and vomiting, and diarrhea was more frequent in the 57-to-63-days group. The overall percentages of events reported as severe were 3 percent for diarrhea, 10 percent for vomiting, and 20 percent for nausea. Medications for these adverse events were taken by 1 percent, 4 percent, and 19 percent of the women, respectively, with no differences among the gestational-age groups. Severe vomiting resulted in one hospitalization and was the reason for one medically indicated surgical intervention.

In the four-hour observation period after the administration of misoprostol, the number of adverse events and the percentage classified as severe were similar to those reported during the entire study period. During these four hours, nausea ($P<0.001$) and vomiting ($P<0.001$) were significantly more frequent in the 50-to-56- and 57-to-63-days groups than in the ≤49-days group, and abdominal pain ($P=0.009$) and diarrhea ($P=0.006$) were more severe in the 57-to-63-days group.

The frequency of adverse events declined significantly with increasing gravidity and parity (Table 2). Nulliparous women received significantly more analgesia ($P<0.001$), opiate analgesia ($P<0.001$), and medications for nausea ($P<0.001$) and diarrhea ($P<0.001$) than parous women. Chronologic age was not consistently related to the frequency of adverse events.

Other adverse events reported included headache (32 percent); dizziness, encompassing light-headedness and faintness (12 percent); back pain and fatigue (9 percent each); fever, vaginitis, and viral infections (4 percent each); rigors and dyspepsia (3 percent each); and asthenia, leg pain, anxiety, insomnia, anemia, syncope, leukorrhea, and sinusitis (2 percent each). Endometritis occurred in 19 women; it was considered study-related in 10, in 1 of whom it was severe.

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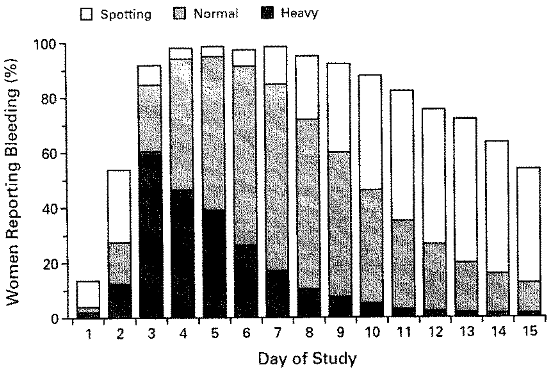

Figure 3. Types of Vaginal Bleeding as Recorded by the Women from Day 1 (Administration of Mifepristone) to Day 15.

The data are from 1506 women who did not undergo surgical termination of pregnancy and who recorded the types of bleeding they had from study day 1 to day 15 on menstrual-diary cards. Bleeding was characterized as spotting, as similar to normal menstrual bleeding (normal), or as heavier than normal menstrual bleeding (heavy).

TABLE 2. INCIDENCES OF ABDOMINAL PAIN, NAUSEA, VOMITING, AND DIARRHEA ACCORDING TO GESTATIONAL GROUP, GRAVIDITY, AND PARITY.

VARIABLE	NO. OF WOMEN	ABDOMINAL PAIN	NAUSEA	VOMITING	DIARRHEA
			number (percent)		
Gestational group					
≤49 days	859	827 (96)	528 (61)	222 (26)	174 (20)
50 to 56 days	722	704 (98)	512 (71)*	277 (38)*	169 (23)
57 to 63 days	540	529 (98)	388 (72)*	220 (41)*	142 (26)†
Gravidity					
1	568	555 (98)	395 (70)‡	236 (42)‡	148 (26)‡
2	527	519 (98)‡	378 (72)‡	205 (39)‡	131 (25)‡
≥3	1026	986 (96)	655 (64)	278 (27)	206 (20)
Parity					
0	1163	1143 (98)	827 (71)	473 (41)	295 (25)
1	449	432 (96)§	280 (62)§	132 (29)§	94 (21)
≥2	509	485 (95)§	321 (63)§	114 (22)§	96 (19)§

*P<0.001 for the comparison with the ≤49-days group (by Fisher's exact test).

†P=0.01 for the comparison with the ≤49-days group (by Fisher's exact test).

‡0.001≤P≤0.03 for the comparison with the women who had had three or more pregnancies (by Fisher's exact test).

§0.001≤P≤0.004 for the comparison with the women who had had no children (by Fisher's exact test).

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DISCUSSION

In this large, multicenter U.S. trial, the success of medical termination of pregnancy decreased gradually with advancing gestational age. We confirmed the international experience that mifepristone and misoprostol can terminate pregnancies of up to 49 days' duration, although the success rate was lower than previously described.[7,10-12] As noted in other countries,[13] this lower success rate may be related to the lack of experience with medical abortion in the United States as well as to the design of our study. We considered the need for surgical intervention on day 15 as representing failure, but abortion might have occurred later.[13,14] Also, a surgical termination performed at the woman's request was classified as a failure instead of being excluded from the efficacy analysis.[10,12,13] Unexpectedly, success was also less frequent among women who had previous elective abortions. Although the reason is unknown, this factor could also have contributed to the differences, because 51 percent of the women in our study had had previous elective abortions, as compared with 25 to 27 percent in two British studies.[12,13]

Efficacy decreased after 49 days' gestation. A similar trend has previously been reported with misoprostol but not with gemeprost.[10-15] Thus, the lower success rates later in gestation are probably related to the prostaglandin component of the regimen. Such lower rates were not found when misoprostol was given by the vaginal route,[16,17] presumably because of greater tissue bioavailability.[18] Higher doses of oral misoprostol increase uterine contractility[19] and are also associated with improved results.[11,12,15] Efficacy is not, however, related to differences in the dose of mifepristone, and similarly good results have been reported with single doses as low as 200 mg.[11,14,20]

The incidence of adverse events rose with the duration of pregnancy.[7,10,13] These events included both subjective symptoms (abdominal pain, nausea, and vomiting) and more objective markers (hospitalizations and surgical interventions). The majority of hospitalizations and surgical interventions were for vaginal bleeding. With advancing pregnancy, the duration of bleeding increased, as did the administration of uterotonic drugs and intravenous fluids. Despite the increases in the numbers of failures and adverse events, the majority of the women in this study reported that they were satisfied with their medical abortions, regardless of whether the outcome was successful (Winikoff B, et al.: unpublished data).

One drawback of this method of pregnancy termination is the inconvenience of the four-hour clinic stay after the administration of misoprostol. In its favor is the fact that many adverse events, including those rated as severe, occurred during this period, as did almost half the expulsions, and some women may prefer to be in the clinic during these events. Moreover, in the women with pregnancies of longer duration, the majority of the hospitalizations or surgical interventions occurred on day 3, whereas in the women with pregnancies of shorter duration, these events were evenly distributed throughout the 15-day study period. Thus, the four-hour visit may be most appropriate for women with pregnancies of longer duration. Nonetheless, on the basis of the results of a small study, mifepristone combined with home application of vaginal misoprostol is a safe alternative in women with pregnancies of up to 56 days' duration.[17]

Careful medical follow-up is essential to ensure that surgical termination is performed in cases of failed medical abortion. In this study, 5 percent of the women did not return for final confirmation of the outcomes of their pregnancies, and five of these women had continuing pregnancies when last seen at visit 2. The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women. In other studies, the loss to follow-up has ranged from 3 to 11 percent.[5-7,10,12,21] Although mifepristone is not teratogenic in rats, mice, or monkeys,[22,23] skull deformities attributed to uterine contractions occurred in rabbits.[24] Misoprostol, on the other hand, has been reported to be teratogenic in humans.[25,26]

Recently, other methods of medical abortion have been evaluated. Oral misoprostol alone is not effective.[19,27] The efficacy of vaginal misoprostol in the first trimester varies widely, from 47 to 94 percent,[28,29] but it is highly effective in the second trimester.[30] Success rates with methotrexate and vaginal misoprostol range from 83 to 98 percent.[31-35] As compared with mifepristone, this latter regimen has the advantage of being an effective treatment for ectopic pregnancy.[36] However, misoprostol has to be given three to seven days after methotrexate, delaying the abortion process.[35] Unlike mifepristone, methotrexate is cytotoxic to proliferating trophoblast tissue, and persisting pregnancies may represent a greater teratogenic risk.[28,32,33,35]

In conclusion, the regimen of mifepristone and misoprostol is safe and effective for women seeking medical abortions of pregnancies of 49 days' duration or less. With longer durations of pregnancy, the regimen is less effective and the incidence of adverse events is higher.

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APPENDIX

The participating principal investigators and their associated centers are listed below (at the investigator's request, Planned Parenthood of Greater Boston is listed by center only):

P. Blumenthal, Johns Hopkins Bayview Medical Center, Baltimore; L. Borgatta, Planned Parenthood of Westchester and Rockland, White Plains, N.Y.; M.D. Creinin, University of Pittsburgh, Pittsburgh; C.L. Dean, Washington University School of Medicine, St. Louis.; S. Haskell, Planned Parenthood of Greater Iowa, Des Moines; T.C. Malloy, Feminist Women's Health Center, Atlanta; D.R. Mishell, Jr., University of Southern California School of Medicine, Los Angeles; M. Nichols and E. Newhall, Oregon Health Sciences University, Portland; Planned Parenthood Clinic of Greater Boston, Boston; A.N. Poindexter, Planned Parenthood of Houston and Southeast Texas, Houston; S.T. Poppema, Aurora Medical Services, Seattle; E. Rothenberg, Planned Parenthood of Central New Jersey, Shrewsbury; K.L. Sheehan, Planned Parenthood of San Diego and Riverside Counties, San Diego, Calif.; L. Sogor, Preterm, Cleveland; J. Tyson, Planned Parenthood of Northern New England, Burlington, Vt.; P. Vargas, Planned Parenthood of the Rocky Mountains, Denver; and C. Westhoff, Columbia University College of Physicians and Surgeons, New York.

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Clostridium sordellii Infection in Medical Abortion

Beverly Winikoff
Gynuity Health Projects, New York, New York

(See the article by Aldape et al. on pages XXX–XX)

> *Doubt is not a pleasant condition, but certainty is absurd.*
>
> —Voltaire

A newly described, rare, lethal entity that affects previously healthy young people and has no known prevention or treatment constitutes a true public health nightmare. It also excites public attention and demands for action. The review of *Clostridium sordellii* infections by Aldape et al. [1] in this issue of *Clinical Infectious Diseases* tells the beginning of an infectious disease story to which epidemiology and clinical medicine have not yet written an ending.

The organism *C. sordellii* is an uncommon human pathogen, although it has been more thoroughly described in veterinary medicine. Recently, several dozen cases of human infection have been reported. The number of cases in the literature has accumulated more rapidly in recent years, suggesting that this condition, like other rare diseases, is more likely to be identified when knowledge of the syndrome is more widely disseminated.

Perhaps the most dramatic of the cases described are those that involved previously healthy young women who succumb to this infection after an obstetric event. Indeed, the cases reported after childbirth, miscarriage, and abortion have been almost uniformly fatal. Furthermore, fatalities due to *C. sordellii* toxic shock syndrome in conjunction with medical abortion, occurring exclusively in the United States, ensured that the name of this previously unfamiliar pathogen would find a place on the front pages of national newspapers and become a part of the "abortion wars" in the halls of Congress.

Thus, there has been some urgency to have credible scientific wisdom to provide the public with answers about where this infection comes from, why it happens, and what we can do to prevent and/or cure it. Unfortunately, as Aldape et al. [1] make clear, we have few answers to offer. With incomplete knowledge, the field has been wide open to speculation and rumor.

With respect to the occurrence of *C. sordellii*-related fatalities after abortion using mifepristone and misoprostol, 6 potential theories for understanding causality and for preventing the disease have been put forward: (1) the pills were contaminated; (2) there has been some kind of mutation in the organism that accounts for the occurrence of these cases now and not elsewhere or previously; (3) mifepristone depresses the immune system, thus setting the stage for this infection; (4) the use of vaginal misoprostol allows women with existing vaginal colonization with *C. sordellii* to develop systemic illness; (5) the vaginal insertion, by women themselves, of misoprostol introduces contamination with *C. sordellii* into the vagina; and (6) the use of prophylactic antibiotics in surgical abortion procedures may account for the absence of such cases after surgical abortion and may be presumed also to be able to prevent this infection after medical abortion.

As noted by Aldape et al. [1], tests of the lots of pills used by the affected women yielded negative results, putting this hypothesis to rest. A new variant of the organism is possible and is consistent, perhaps, with apparent changes in the virulence of the related organism, *Clostridium difficile*. Such a change may also be consistent with the geographic specificity of these cases to North America—and, specifically with regard to the United States, to California [2]. But it does not explain any particular relationship to medical abortion.

Studies of animals revealing immune system effects of mifepristone have been cited, along with fairly elaborate hypo-

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Reprints or correspondence: Dr. Beverly Winikoff, Gynuity Health Projects, 15 E. 26th St., Ste. 1617, New York, NY 10010 (bwinikoff@gynuity.org).

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thetical (but as yet unobserved) clinical pathways by which mifepristone might affect the immune system in humans. On the other hand, there are several larger-picture facts that seem to speak against the importance of this theory. In the first place, the drug is given as a one-time 200-mg dose for abortion. Yet, in experimental long-term use for chronic diseases (e.g., meningioma, fibroids, and ovarian cancer), no such infections have been recorded. Furthermore, in Europe, where the drug has been in use since 1988, the usual dose has been 600 mg (3 times the dose in the United States), but no cases of *C. sordellii* toxic shock have been reported there. In addition, none of the women who died of *C. sordellii* toxic shock after childbirth or spontaneous abortion had received any mifepristone at all. And finally, it is hard to imagine a biological effect in which a drug-induced alteration of the immune system would result in the appearance of only 1 specific infection at a rate of ~0.7 cases per 100,000 users and no other immune effects.

Vaginal use of the misoprostol has also been suggested as a potential causal factor in these events. But with respect to medical abortion, it is not surprising that the 4 women in the United States who developed this condition after medical abortion had used misoprostol vaginally, because almost all use of mifepristone in the United States through mid-2006 involved vaginal misoprostol. If we apply the estimate that 0.1%–0.5% of women may be carriers of this organism [3, 4] to the fact that >600,000 US women have undergone medical abortions, most of which involved vaginal misoprostol, it suggests that somewhere between 600 and 3000 women would have used the medication in the presence of vaginal colonization with *C. sordellii*. However, only 4 infections have occurred in the United States, and because the infections are uniformly fatal, in the context of hypervigilance about abortion events, we can be quite certain that this number is accurate.

Indeed, vaginal use of misoprostol has been standard in the United Kingdom, Sweden, and South Africa, and no cases of *C. sordellii* toxic shock have been reported from those countries. As a matter of fact, a review of all infections after various regimens of medical abortion demonstrated that infection generally occurred very infrequently but was reported more frequently in studies from the United Kingdom than in studies from outside the United Kingdom (including the United States) and was unrelated to the route of administration of misoprostol [5].

If women were introducing contamination into the vagina by self-application of the misoprostol in the United States, we would expect to see many more of the common infections that result from contamination by skin and fecal bacteria. Yet, such infections are rarely reported in conjunction with medical abortions in the United States, and as noted above, post–medical abortion infection has generally been a less common condition among patients in US studies than among patients in studies from the United Kingdom, where health service providers (and not the women) insert the vaginal misoprostol.

Finally, there is no compelling evidence that prophylactic antibiotics would be effective in preventing these medical disasters. Moreover, the antibiotic treatment would have to be applied (with all the attendant risks of adverse effects) to ~140,000 women who did not need treatment, to prevent 1 case of infection. Indeed, even considering the costs and risks of such mass treatment and the problems caused by overuse of antibiotic therapy generally, there are some clinicians who would be ready to proceed with such prophylaxis. But other voices have been raised in alarm about this idea. As for clinical studies of the value of this approach, these appear to be out of the question logistically and financially. With such a rare event, estimates of the number of patients required for an adequate clinical trial have ranged from 80,000 to well over 100,000, depending on the assumptions made.

A large natural experiment is now occurring in this country that may provide the best chance of learning more (although probably not definitive) information about some of these causal hypotheses. Until mid-2006, when almost all mifepristone abortions were accompanied by use of vaginal misoprostol, the rate of *C. sordellii* infection after medical abortion appeared to be ~0.7 cases per 100,000 procedures. In 2006, with a great deal of public attention to these deaths, some large clinic systems—including, notably, Planned Parenthood clinics—and many independent providers decided to stop using misoprostol vaginally and to advise oral or buccal use of this medication after use of mifepristone. We will have to wait, perhaps many months or years, but eventually we may see whether this change in practice is accompanied by any measurable change in the rate of these tragic deaths. And even if, with passage of time, there is a suggestion of some impact, we still will not have a complete explanation of this complex epidemiological and clinical situation. In the mean time, we will need to learn to live with our uncertainties and avoid the mistakes so easily caused by acting on assumptions and guesses rather than facts.

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Potential conflicts of interest. All authors: no conflicts.

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REVIEW ARTICLE

Clostridium sordellii Infection: Epidemiology, Clinical Findings, and Current Perspectives on Diagnosis and Treatment

M. J. Aldape,[1,2] A. E. Bryant,[1,2] and D. L. Stevens[1,3]

[1]Veterans Affairs Medical Center, Boise, and [2]University of Idaho, Moscow, Idaho; and [3]University of Washington School of Medicine, Seattle

(See the editorial commentary by Winikoff on pages XXX–XX)

Clostridium sordellii **infections pose difficult clinical challenges and are usually fatal. Most commonly, these infections occur after trauma, childbirth, and routine gynecological procedures, but they have recently been associated with medically induced abortions and injection drug use. We report 2 fatal cases, one of which was associated with minor trauma, and the other of which was associated with normal childbirth, and we summarize the clinical features of 43 additional cases of reported** ***C. sordellii*** **infection. Of these 45 cases, 8 (18%) were associated with normal childbirth, 5 (11%) were associated with medically induced abortion, and 2 (0.4%) were associated with spontaneous abortion. The case-fatality rate was 100% in these groups. Ten (22%) of the** ***C. sordellii*** **infections occurred in injection drug users, and 50% of these patients died. Other cases of** ***C. sordellii*** **infection (in 19 patients [43%]) occurred after trauma or surgery, mostly in healthy persons, and 53% these patients died. Overall, the mortality rate was 69% (31 of 45 patients). Eighty-five percent of all patients with fatal cases died within 2–6 days of initial infection, and nearly 80% of fatal cases developed leukemoid reactions. Rapid diagnostic tests and improved treatments are needed to reduced the morbidity and mortality associated with this devastating infection.**

INTRODUCTION, HISTORICAL PERSPECTIVE, MICROBIOLOGY

Clostridium sordellii was first isolated in 1922 by the Argentinean microbiologist Alfredo Sordelli [1], who named it *Bacillus oedematis sporogenes* on the basis of its morphology and the marked tissue edema characteristic of infection. In 1927, the organism was renamed *Bacillus sordellii* [2]. Two years later, it was shown to be identical to *Clostridium oedematoides* [3, 4], and the name *C. sordellii* was adopted. Similarities in morphology and biochemical profile suggested that *C. sordellii* was simply a virulent strain of *Clostridium bifermentans;* however, urease production by *C. sordellii* clearly distinguished the 2 species [5]. In the late 1970s, *C. sordellii* antitoxin was found to neutralize the cytotoxic effect of stool specimens collected from patients with *Clostridium difficile*–associated pseudomembranous colitis [6–9]. It was later shown that virulent isolates from both species produced a common cytotoxin (see Pathogenesis).

C. sordellii is an anaerobic, gram-positive, spore-forming rod with peritrichous flagella. Colonies appear translucent to opaque with small zones of β hemolysis on sheep or rabbit blood agar. The organism is commonly found in the soil and in the intestines of animals, including 0.5% of all humans [10]. Many of the strains are nonpathogenic; however, virulent strains cause lethal infections in several animal species, such as enteritis and enterotoxaemia in sheep and cattle [11–14] and myonecrosis and gangrene in humans (table 1). Virulence is attributed to numerous exotoxins, although only 2, the lethal and hemorrhagic toxins, have been extensively studied (see Pathogenesis).

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Reprints or correspondence: Dr. Michael Aldape, Veterans Affairs Medical Center, Infectious Diseases Section, 500 West Fort St., Bldg. 45, Boise, ID 83702 (maldape32@hotmail.com).

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Table 1. **Summary of characteristics reported for *Clostridium sordellii* infection.**

Patient	Age[a]/sex	Basis of infection	Temperature, °C	WBC count, cells/mm^3	Refractory hypotension	Other organisms isolated	Outcome	Reference
1	4/M	Arm trauma	Afebrile	41,200	Yes	Yes	Died	PR
2	39/F	Childbirth	37.2	123,400	Yes	Yes	Died	PR
3	28/F	Childbirth	36.1	84,200	Yes	Yes	Died	[15]
4	23/F	Childbirth	35.8	66,000	Yes	Yes	Died	[15]
5	23/F	Childbirth	Afebrile	93,600	Yes	Yes	Died	[15]
6[b]	29/F	Childbirth	Afebrile	115,000	Yes	No	Died	[16]
7	24/F	Childbirth	36.1	200,000	Yes	Yes	Died	[17]
8	24/F	Childbirth	38.7	84,900	Yes	Yes	Died	[18]
9	40/F	Childbirth	Afebrile	105,400	Yes	Yes	Died	[19]
10	18/F	MIA	Afebrile	158,000	Yes	Yes	Died	[20]
11	21/F	MIA	38.9	NA	Yes	Yes	Died	[20]
12	22/F	MIA	36.2	120,200	Yes	Yes	Died	[20]
13	34/F	MIA	Afebrile	87,600	Yes	Yes	Died	[20]
14	26/F	MIA	"Normal"	20,000	Yes	Yes	Died	[21]
15	NA/F	Spontaneous abortion	NA	NA	NA	Yes	Died	[22]
16	NA/F	Spontaneous abortion	NA	NA	NA	NA	Died	[22]
17	39/F	Endometritis	Afebrile	19,000	Yes	No	Died	[23]
18	28/F	Injection drug use	37	29,800	NA	Yes	Died	[24]
19	NA/M	Injection drug use	Afebrile	58,800	Yes	NA	Died	[25]
20[c]	47–57/NA	Injection drug use	36.1	61,600	Yes	Yes	Died	[26]
21[c]	47–57/NA	Injection drug use	36.1	61,600	Yes	No	Died	[26]
22[c]	47–57/NA	Injection drug use	36.1	61,600	Yes	Yes	Died	[26]
23[c]	25–45/NA	Injection drug use	37.1	32,300	No	Yes	Survived	[26]
24[c]	25–45/NA	Injection drug use	37.1	32,300	No	Yes	Survived	[26]
25[c]	25–45/NA	Injection drug use	37.1	32,300	No	Yes	Survived	[26]
26	52/M	Injection drug use	38	12,000	No	No	Survived	[24]
27[b]	37/M	Injection drug use	38.2	19,000	No	No	Survived	[27]
28	23/M	Leg trauma	38.4	40,000	Yes	No	Died	[28]
29[b]	81/F	Soft-tissue tear	36.7	19,000	Yes	NA	Died	[29]
30	37/M	Foot trauma	37	9200	No	Yes	Survived	[30]
31	42/M	Hand trauma	37.5	13,000	No	No	Survived	[31]
32	NA/F	Hysterectomy	41.1	NA	Yes	Yes	Died	[32]
33[b]	48/F	Liver transplantation	39.4	NA	Yes	Yes	Died	[33]
34[b]	55/M	Cystectomy	39	21,000	Yes	NA	Died	[34]
35	23/M	Tissue allograft	NA	NA	NA	No	Died	[35]
36	33/M	Ocular surgery	NA	NA	No	NA	Survived	[36]
37	17 days/F	Omphalitis	35.5	37,400	NA	Yes	Died	[37]
38[b]	61/M	Endocarditis	38.3	12,700	No	No	Survived	[38]
39[b]	NA	Endocarditis	NA	NA	NA	NA	Survived	[39]
40[b]	NA	Endocarditis	NA	NA	NA	NA	Survived	[39]
41[b]	12/M	Ear infection	38.4	10,900	No	NA	Survived	[29]
42	38/M	Knee infection	37.8	9800	No	No	Survived	[40]
43	30/F	Medicinal injection	40.4	58,200	Yes	Yes	Died	[41]
44	95/F	Empyema	36.6	13,500	NA	Yes	Died	[42]
45	55/M	Empyema	38.6	19,200	No	No	Survived	[43]

NOTE. MIA, medically induced abortion; NA, not available; PR, present report.

[a] Age is in years, unless otherwise indicated.

[b] Patient had bacteremia.

[c] Highest values were chosen from the temperature and WBC count ranges provided in [26].

ILLUSTRATIVE CASE REPORTS

Patient 1. A 4-year-old boy presented to the emergency department after sustaining a closed transverse fracture of the arm. Vital signs were normal, and the patient was afebrile. After application of a long arm cast, the patient was discharged while receiving acetaminophen with codeine. Within 24 h, severe pain and swelling in the affected arm and fingers prompted his hospital admission. Intravenous cefazolin therapy was commenced, and the patient was taken to the operating room. Muscle compartment pressures were elevated, and muscles of the hand were "blackened." After a volar fasciotomy of the superficial and deep compartments of the left forearm, the arm was dressed and fixed with an external splint. Tissues samples were sent for culture. Postoperatively, the patient remained afebrile, with a blood pressure of 128/82 mm Hg, but the pulse increased to 150 beats/min. Color returned to his fingers, and the patient was able to wave them to his mother.

Twelve h after surgery, the patient's pulse increased to 164 beats/min, and his blood pressure decreased to 108/60 mm Hg, but he remained afebrile. The left forearm became grossly swollen, and both lower extremities were cool. Intravenous vancomycin treatment was started. The WBC count was 31,900 cells/mm^3 (figure 1), with 77% segmented neutrophils, 6% bands, 12% lymphocytes, and 5% monocytes; the hematocrit was 42.9%, and the platelet count was 210,000 platelets/mm^3. Gentamicin and piperacillin were administered. A second surgery revealed necrotic and foul-smelling muscle, fat, and fascia, with complete cessation of blood flow to the wrist. Tissue specimens obtained during both surgeries revealed large, gram-positive rods subsequently identified as *C. sordellii.*

The next morning, the WBC count increased to 41,200 cells/mm^3 (figure 1), with 45% segmented neutrophils, 7% band cells, 2% myelocytes, 1% metamyelocytes, 33% lymphocytes, and 12% monocytes. The hematocrit was 41.9%. By mid-afternoon, the boy became hemodynamically unstable, with increasing hypotension, tachycardia, metabolic acidosis, and decreased urine output. Hours later, ultrasound-guided pericardiocentesis produced 75 mL of straw-colored fluid. Refractory hypotension developed, and despite intensive efforts, the patient died.

The autopsy reported generalized soft-tissue edema and a large collection of fluid in both pleural spaces and the peritoneal cavity. Histopathologic examination of the affected arm revealed severe soft-tissue necrosis, with interstitial hemorrhage and neutrophilic infiltrates in the connective tissue. No evidence of vascular thrombosis was observed.

Patient 2. A previously healthy, 21-year-old woman sustained a third-degree vaginal laceration during delivery of her second child. The wound was sutured, and 4 days later, she developed chills, difficulty urinating, and increasingly severe perineal pain that radiated into her buttocks and right thigh. On presentation to the emergency department, her vital signs were as follows: temperature, 37.2°C; blood pressure, 96/57 mm Hg; pulse, 132 beats/min; and respiratory rate, 20 breaths/min. Significant laboratory findings included the following: serum bicarbonate level, 18 mmol/L; creatinine level, 0.7 mg/dL; glucose level, 100 mg/dL; total protein level, 5.8 g/dL; and albumin level, 2.1 g/dL. Prothrombin and partial thromboplastin times were 12.2 and 33.7 s, respectively. The patient's initial hematocrit was 48.3%, her platelet count was 242,000 platelets/mm^3, and her WBC count was 67,000 cells/mm^3 (figure 1), with 74% segmented neutrophils, 14% bands, 8% monocytes, and 4% lymphocytes. She remained tachycardic, and the findings of auscultation of her chest were unremarkable. The perineum was bluish-gray in color, and the labia were edematous. Intravenous gentamicin and clindamycin were started. CT of the pelvis and abdomen revealed only peritoneal fluid and an enlarged uterus.

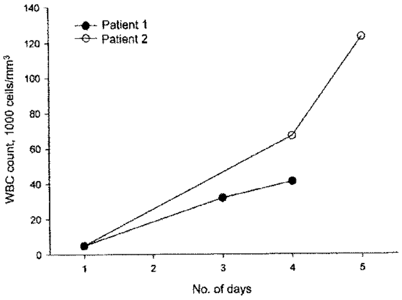

Figure 1. Dynamics of the leukemoid reactions in the 2 cases of *Clostridium sordellii* infection detailed in this review.

Surgical debridement and fasciotomy of the vulva were performed. Vancomycin was added to the antibiotic regimen. Postoperatively, the WBC count increased to 123,400 cells/mm^3 (figure 1), with 48% segmented neutrophils, 40% bands, 3% myelocytes, 1% metamyelocytes, 4% monocytes, and 3% lymphocytes. Nucleated RBCs were also present, and the platelet count was reduced (141,000 platelets/mm^3). Hypotension persisted, profound metabolic acidosis (pH 7.15) ensued, and hypomagnesemia (magnesium level, 0.9 mmol/L) and hypocalcemia (calcium level, 7.26 mmol/L) developed. Antibiotics, sodium bicarbonate, magnesium sulfate, and copious quantities of intravenous fluids were administered. Shortly after surgery, her heart rate increased to 160–170 beats/min, cardiac arrest ensued, and she died.

Bacterial culture of specimens of the debrided perineal tissue yielded heavy growth of *C. sordellii* and moderate growth of *Clostridium perfringens, Prevotella loeschii,* and additional mixed anaerobic flora. Blood culture results were negative. At autopsy, the vulva was edematous and erythematous. The pericardial space and the right and left pleural cavities contained 80, 400, and 250 mL of clear, straw-colored fluid, respectively. Microscopically, moderate vascular congestion was noted in the lungs, liver, adrenal glands, and kidneys. The myometrium was hypertrophic and hyperplastic, with fibrin thrombi in the blood vessels of the endometrium. The cervix was markedly congested with edema and chronic inflammation. Histopathologic examination of the uterine tissue revealed large, rod-shaped organisms and modest numbers of inflammatory cells in various stages of degeneration (figure 2).

EPIDEMIOLOGY OF *C. SORDELLII* INFECTION

C. sordellii *infection after natural childbirth and spontaneous abortion.* A literature search was performed for reported cases of *C. sordellii*, *B. sordellii*, and *B. oedematis sporogenes* infections using the Index Medicus, Pubmed, and Medline databases over the period of 1927–2006. The search produced 29 reports describing 43 patients (table 1). These patients, plus the 2 described here, bring the total cases for analysis to 45 (table 1). Of the cases reviewed in which the patient's sex was specified, most (23 [63%] of 37) *C. sordellii* infections occurred in women with a mean age of 33.6 years (tables 1 and 2). Of these, 8 (35%) of 23 cases were associated with normal childbirth [15–19, 23], 5 (22%) were associated with medically induced abortion (MIA) [20, 21], and 2 (9%) were associated with spontaneous abortion [22] (table 1). The mortality rate was 100%. *C. sordellii* was implicated in all cases, but it was the sole pathogen in only 2 of these cases. Other organisms isolated included *C. perfringens*, *Escherichia coli*, staphylococcal and streptococcal species, and a variety of other anaerobes and coliforms.

The source of *C. sordellii* in obstetric/gynecological-associated infections is unknown, although 2 reports have documented prolonged vaginal carriage of *C. sordellii* in 0.5%–10% of healthy women [44, 45], suggesting that some women may be natural *C. sordellii* carriers. The rate of vaginal colonization with a variety of *Clostridium* species during the period after childbirth or abortion is reportedly as high as 29% [46, 47]. Alternatively, fecal contamination of the vagina during vaginal delivery could provide a source of organisms that could infect vaginal tears or the episiotomy site or ascend to the uterus through the open cervix. However, no *C. sordellii*–related deaths have been reported following instrumented abortion or routine dilatation and curettage, both of which require opening of the cervix, perhaps because fecal contamination of the vagina in these settings is less likely.

C. sordellii *infection after MIAs.* Mifepristone (RU-486; Danco Laboratories) has been used worldwide as a birth control alternative. Mifepristone inhibits the action of progesterone by blocking glucocorticoid receptors and is used in conjunction with misoprostol, a synthetic prostaglandin that stimulates heavy vaginal secretion. These agents cause the uterine lining to slough, preventing implantation. Nearly 2 million women in Europe have used mifepristone, and no *C. sordellii* infections or deaths have been reported [45]. In addition, since the year 2000, more than 600,000 women in the United States have undergone mifepristone-induced abortion. There have been 5 reported *C. sordellii*–related deaths worldwide due to mifepristone-associated MIA (table 1), and all occurred in North America. This equates to ~1 death per 120,000 patients in North America [45]. Investigators have failed to identify any specific factor that predisposed these women to fatal infection. Interestingly, 80% of reported *C. sordellii*–related deaths occurred in the state of California. The regional nature of these fatalities suggested that the medication may be contaminated with *C. sordellii*, but this was proved not to be the case. Misuse of misoprostol—specifically, intravaginal administration—may also be to blame and is currently under investigation [48].

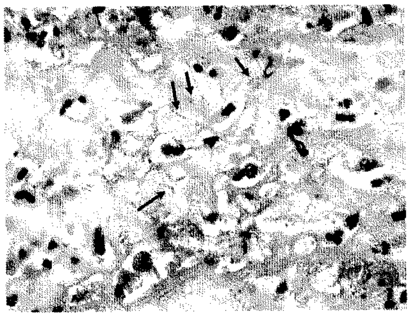

Figure 2. Histopathologic findings for tissue specimens collected at the site of infection from a patient with fatal *Clostridium sordellii* infection (patient 2). Numerous gram-positive bacilli *(arrows)* and degenerating inflammatory cells are apparent within the tissue (hematoxylin and eosin staining; original magnification, ×100).

The association between lethal *C. sordellii* infection and MIA raised concerns of mifepristone's safety. On 19 July 2005, the US Food and Drug Administration issued a public health advisory regarding *C. sordellii*–associated deaths involving mifepristone/misoprostol-induced MIA [49]. As with many rapidly fatal diseases, prevention is paramount. The manufacturer of mifepristone has recently provided information for patients and health care providers warning that *C. sordellii* infections may have unusual manifestations and that delays in treatment can result in fatal outcomes [50]. Prohibiting vaginal administration of misoprostol has also been suggested as a preventative measure [48].

Potential pathogenic mechanisms have only recently been

Table 2. **A comparison of demographic and clinical features among survivors and nonsurvivors of *Clostridium sordellii* infection.**

Characteristic	Survivors (n = 14)	Nonsurvivors (n = 31)
Age, mean years (range)	39.3 (12–61)	34.6 (0–95)
Sex, no. of patients		
Female	0	23
Male	9	5
Unknown	5	3
Temperature, mean °C (range)[a,b]	37.7 (37–38.6)	37.3 (35.3–41.1)
WBC count, mean cells/mm^3 (range)[b]	18,459 (9200–32,300)	75,240 (19,000–200,000)[c]

[a] Afebrile patients and those with normal temperatures were given a value of 37°C for calculations.

[b] Unknown vital values were not incorporated into determined averages.

[c] Statistically different value for survivors ($P < .05$, by paired t test).

suggested. Mifepristone/misoprostol may facilitate colonization of uterine tissue, trigger toxin expression, or induce hypotension and systemic shock by dysregulating the host's immune response. These and other mechanisms are actively being investigated.

C. sordellii ***infection in injection drug users.*** Several studies of fatal *C. sordellii* soft-tissue infection in injection drug users in Europe and North America have been published [24–26, 51]. In our review, 10 (22%) of 45 reported *C. sordellii* infections fell into this category. Of these, 50% were fatal (table 1). In 1999, an outbreak of necrotizing soft-tissue infection occurred in California stemming from "skin popping" of black tar heroin. *C. sordellii* was identified in 6 of 9 wound specimens, and 4 of 9 patients died [26]. Two similar outbreaks of infection were also reported in the San Francisco, California, area during 1992–1997 and again in 1999; *C. sordellii* was isolated in 4 of 9 and 2 of 5 patients, respectively [24, 51]. During 2000–2004, nearly 200 cases of soft-tissue infection in injection drug users were reported in the United Kingdom. Nearly 95% of the infections requiring hospitalization were caused by clostridial species, including *C. sordellii* [25]. It was postulated that the drug paraphernalia or the drugs "cut" with soil were contaminated with spores. In either case, repeated injection of drugs into the subcutaneous tissue likely resulted in local ischemia that provided an anaerobic environment favorable to the germination and outgrowth of clostridial spores.

Other* C. sordellii *infections. *C. sordellii* infections were by no means limited to gynecological procedures and illicit drug use (table 1). In fact, 19 (42%) of 45 cases of *C. sordellii* infection occurred after nongynecological surgical procedures or penetrating, crush, or traumatic injuries to the soft tissues in previously healthy men, women, and children (table 1). Of these 19 patients, 10 (53%) died.

Three reports, including our own, described *C. sordellii* infections in children. One involved a 17-day-old infant who developed neonatal toxic omphalitis [37] and died, despite having received 6 days of aggressive treatment that included multiple debridements and broad-spectrum antibiotic therapy. Both umbilical tissue and peritoneal fluid collected at surgery grew *C. sordellii;* no complications were reported involving the mother. The other patient described was a 12-year-old boy who developed *C. sordellii* sepsis after an ear infection but survived after an intensive 2-week course of antibiotic therapy and supportive care [29].

Numerous postsurgical *C. sordellii* infections have occurred after hysterectomy, musculoskeletal-tissue allograft, liver transplantation, prostate surgery, and eye surgery [32, 33, 35, 36, 52]. *C. sordellii* infections have also been reported after traumatic, penetrating injures to the foot and leg [28, 30]. "Spontaneous" *C. sordellii* infections were also reported in patients with underlying conditions, such as alcoholism with liver cirrhosis, malignancies, and immunosuppression [34, 53–55]. In these cases, patients had no obvious portals of entry, yet all developed lethal *C. sordellii* infections. Indeed, spontaneous infections in compromised individuals have also been reported with other clostridial species (e.g., *Clostridium septicum* and *C. difficile*). Other reported *C. sordellii* infections included pneumonia, empyema, septic arthritis, and endocarditis [38–43].

SUMMARY OF CLINICAL FEATURES OF *C. SORDELLII* INFECTION

Early clinical symptoms of infection include nausea, dizziness, lethargy, and mild tenderness or rash at sites of infection. Most patients (73%) were afebrile (table 3). Within hours after presentation to the hospital, patients have developed hypotension and tachycardia. Laboratory tests have demonstrated elevated hematocrit, increased WBC and platelet counts, and decreased serum calcium and protein levels. As infections progressed, 6 distinctive clinical features developed that, in total, are unique to *C. sordellii* infection: a marked leukocytosis termed the "leukemoid reaction," refractory hypotension, severe tachycardia, profound capillary leak syndrome, hemoconcentration, and a persistent absence of fever. Specifically, the leukemoid reaction

Table 3. Symptoms and characteristics reported in fatal cases of *Clostridium sordellii* infection.

Characteristics of *C. sordellii* infection	No. (%) of patients with fatal cases who had the indicated feature[a] (n = 26)
Initial symptoms	
Onset of symptoms within 2–6 days	22 (84.6)
Decreased blood pressure	19 (73.1)
Nausea and/or vomiting	11 (42.3)
Dizziness	11 (42.3)
Generalized weakness	11 (42.3)
Diarrhea	5 (19.2)
Blue-colored/pale skin	3 (11.5)
Chills	2 (7.7)
Clinical features	
Septic shock	23 (88.5)
Mild pain associated with site of infection	21 (80.8)
Leukemoid reaction	20 (76.9)
Afebrility	19 (73.1)
Tachycardia	19 (73.1)
Hemoconcentration	16 (61.5)
Pulmonary, peritoneal, or visceral edema	16 (61.5)
Reduced serum protein levels	13 (50.0)
Metabolic acidosis	9 (34.6)
Thrombocytopenia	7 (26.9)
RBCs and WBCs in urine	4 (15.4)
Treatments during course of infection	
Antibiotic treatment	25 (96.2)
Copious intravenous fluids and/or plasma	19 (73.1)
Debridement/surgical procedures	16 (61.5)
Sodium bicarbonate and vasopressor treatment	12 (46.2)
Administration of other complementary therapies such as steroids, morphine, and/or atropine	11 (42.3)
Supplemental oxygen	5 (19.2)
Microbiologic findings	
Identification of *C. sordellii* from infection	26 (100)
Isolation of other bacterial species	19 (73.1)
Isolation of *C. sordellii* from blood	6 (23.1)
Clostridial antigens detected in localized blood vessels	4 (15.4)
Findings at autopsy	
Regions of local necrosis and acute inflammation	20 (76.9)
Marked soft-tissue and/or visceral edema	19 (73.1)
Pericardial, pleural, or peritoneal effusions	19 (73.1)
Thrombosis of localized blood vessels	9 (34.6)
Heavy neutrophil degeneration at margins of necrotic tissue	6 (23.1)

[a] Three injection drug users from the study by Kimura et al. [26] and 2 patients who experienced spontaneous abortion in the study by Chang et al. [22] were not included in the analysis because of a lack of specific data.

has been defined as a WBC count >50×10^3 cells/mm^3 resulting from an acute condition, such as infection [56]. With *C. sordellii* infection, WBC counts routinely increased acutely (within 48–72 h) to 100×10^3 cells/mm^3 of whole blood, with 1 reported case as high as 200×10^3 cells/mm^3 (table 1) [17]. A similar leukemoid reaction is also characteristic of *C. difficile* and *Clostridium novyi* infections [57, 58]. Differential cell counts revealed increased percentage of mature and immature neutrophils (i.e. band cells, metamyelocytes, and myelocytes) [56] and an increase in the absolute numbers of both lymphocytes and monocytes.

The markedly elevated WBC count was highly predictive of fatal outcome. On average, those who died from *C. sordellii* infection had a WBC count of >75,000 cells/mm^3, compared

Table 4. Comparative exotoxins among species that produce large clostridial cytotoxins.

Species, toxin produced	Activity
Clostridium sordellii	
Lethal toxin[a]	Inhibits signaling proteins Rac, Cdc42, Ras, and Rap
Hemorrhagic toxin[a]	Inhibits signaling proteins Rho, Rac, and Cdc42
Hemolysin	Cholesterol-dependent hemolysin
Neuraminidase	Cleaves sialic acids from sialoglycoconjugates
Phospholipase C	Hydrolyzes lecithin
DNAse	Potential degeneration of host cell nuclei
Hyaluronidase	Splits hyaluronic acid, increasing permeability
Collagenase	Hydrolyzes collagen and gelatin
Clostridium difficile	
Toxin A[a]	Inhibits signaling proteins Rho, Rac, and Cdc42
Toxin B[a]	Inhibits signaling proteins Rho, Rac, Cdc42
Binary toxin	Actin-specific ADP-ribosyltransferase
Hyaluronidase	Splits hyaluronic acid, increasing permeability
Collagenase	Hydrolyzes collagen and gelatin
Clostridium novyi	
Types A and B: α-toxin[a]	Inhibits signaling proteins Rho, Rac, and Cdc42
Type A	
γ-Phospholipase C	Hydrolyzes lecithin
Hemolysin	Cholesterol-dependent hemolysin
Types B and D	
Tropomyosinase	Breaks down tropomyosin and myosin
β-Phospholipase C	Hydrolyzes lecithin; human RBC hemolysin
Type D: lipase	Hydrolyzes fats into glycerol and fatty acids

NOTE. ADP, adenosine diphosphate.

[a] Indicates large clostridial cytotoxin.

with only 18,000 cells/mm^3 among survivors ($P < .05$) (table 2). In 4 fatal cases, WBC counts were only 13,500–19,000 cells/mm^3; however, in 2 of these patients, WBC counts were only obtained at hospital admission, and no repeated complete blood cell count data were reported; the other 2 cases were associated with unusually prolonged illnesses (3 and 5 weeks, respectively) in compromised individuals.

Along with the increasing WBC counts, severe tachycardia and tachypnea were frequently described, and subsequent peritoneal and pleural effusions were common. This capillary leak likely contributed to markedly elevated hematocrits and may have resulted from toxin-mediated changes to the vascular endothelium (see Pathogenesis). Most patients who died (19 of 26) remained afebrile throughout the disease course (tables 2 and 3), and no differences in mean temperatures were noted between survivors and nonsurvivors (37.7°C vs. 37.3°C respectively; table 2). Reasons for this lack of fever have not been investigated.

Overall, the mortality rate for patients with *C. sordellii* infection was nearly 69% (table 1), and most patients died of hypotension and multiorgan failure within days to hours after the initial presentation. Postmortem findings included soft-tissue necrosis at the site of infection and visceral edema. On microscopic examination, infected tissues displayed acute inflammatory changes and localized thrombosis of blood vessels. Often, the margin between healthy and necrotic tissue contained heavy neutrophil degeneration. In all cases but 1, *C. sordellii* was identified at the site of infection, and in 9 of 45 cases, *C. sordellii* was found in the blood (table 1).

PATHOGENESIS

The role of* C. sordellii *toxins in pathogenesis. Pathogenic strains of *C. sordellii* produce up to 7 identified exotoxins [1]. Of these, lethal toxin (LT) and hemorrhagic toxin (HT) are regarded as the major virulence factors. Other exotoxins include an oxygen-labile hemolysin, neuraminidase, DNase, collagenase, and lysolecithinase (table 4). The roles of these toxins in pathogenesis have not been extensively investigated.

The family of large clostridial cytotoxins. In 1969, Arseculeratne et al. [59] demonstrated that intramuscular injection of crude *C. sordellii* toxins into guinea pigs produced local necrosis, progressive edema, and terminal shock—symptoms similar to those found in human cases of *C. sordellii* infection (this review). These authors suggested that the lethal effects were the result of 2 factors: an edema-producing, lethal toxin and an extractable hemorrhagic toxin [59].

LT and HT are members of the large clostridial cytotoxin (LCC) family [60, 61], all members of which have molecular weights of 250–308 kDa. Other members include the *C. difficile* toxins A and B and *C. novyi* α-toxin (table 4). All LCCs possess remarkable amino acid similarity, with identities of 26%–76%. LT and *C. difficile* toxin B have the highest homology with amino acid sequences, being 76% identical and 90% homologous to one another.

All LCCs possess glycosyltransferase activity, utilizing UDP-glucose or *N*-acetylglucosamine as their cosubstrate to modify members of the Rho GTPase signaling superfamily [62, 63]. These GTPases control cell cycle, apoptosis, gene transcription [64–66], and the structural functions of actin, such as cell morphology, migration, and polarity [67, 68]. Specifically, *C. difficile* toxins A and B, HT from *C. sordellii,* and the *C. novyi* α-toxin UDP-glycosylate the hydroxyl group of threonine-35 in Rac, Cdc42, or Ras (or threonine-37 in Rho) [69, 70]. These critical threonine residues are found in the effector region of these signaling proteins and are highly conserved among all small GTPase molecules and in some heterotrimeric G proteins [71, 72]. The threonine targets are exposed only in the molecule's inactive GDP-bound state. Once modified, these proteins become inoperative. In the case of Rho, Rac, and Cdc42, modification impairs actin cytoskeletal assembly and organization, presumably leading to the massive capillary leakage characteristic of *C. sordellii* infection. LT from *C. sordellii* is the only LCC with unique targets, modifying Rac, Cdc42, and members of the Ras signaling family, including Ras, Ral, and Rap [73]. Interestingly, Jank et al. [74] have recently shown that change of a single amino acid residue (ser 6 phe) at position 73 converts RhoA into a substrate for LT. Furthermore, Mesmin et al. [75] demonstrated that the glucosyltransferase domain of LT binds preferentially to phosphatidylserine liposomes, suggesting that this avidity directs the toxin to the inner leaflet of the cell membrane where the targets for LT-mediated modification are abundant. A recent study by Waschke et al. [76] demonstrated significant increases in rat microvessel permeability after treatment with *C. sordellii* LT, suggesting that LT may also play a role in systemic capillary leak.

Two putative receptors for Toxin A from *C. difficile* have been suggested: galactose-β1-4-*N*-acetylglucosamine [77] and an unidentified glycosphingolipid [78]. Although the receptors have not been clearly identified or characterized, it is known that toxins enter host cells through an endosomal pathway [61]. The low endosomal pH generates a conformational change in the LCC structure, resulting in insertion and translocation of the toxin's enzymatic region into the cytosol [61]. Reduced pH may also trigger toxin gene expression in *C. sordellii* or increase the activity of *C. sordellii* toxins. For instance, Qa'Dan et al. [79] demonstrated that the cytotoxic activity of LT is increased 5-fold in an acidic environment (pH 4.0–5.0) in vitro. Furthermore, Voth et al. [80] have shown that LT is irreversibly dissociated into active polypeptides at low pH. Although some environments with reduced pH are frequent sites of *C. sordellii* infection (e.g., the normal vagina and injured tissues with inadequate perfusion), a role of pH-dependent cytotoxicity in pathogenesis remains to be verified.

Finally, although the leukemoid reaction is a remarkable clinical feature of *C. sordellii* infection, nothing is known regarding the underlying mechanisms. Ras GTPases control cell differentiation and proliferation [81, 82], and by their modification, LT may play a role in the characteristic leukemoid reaction, although this has yet to be investigated. The similar leukemoid reactions in *C. difficile* and *C. novyi* infections suggest that a common toxin may be responsible.

CURRENT PERSPECTIVES ON DIAGNOSIS AND TREATMENT

Clinical clues and diagnosis. Early diagnosis of *C. sordellii* infection often proves to be difficult for several reasons. First is the low prevalence of these infections. Second, the initial symptoms are nonspecific and, frankly, misleading (table 3). Early in the course, the illness resembles any number of infectious diseases, including viral syndromes. Given these vague symptoms and an absence of fever, physicians usually do not aggressively pursue additional diagnostic tests. The absence of local evidence of infection and the lack of fever makes diagnosis of *C. sordellii* infection particularly problematic in patients who develop deep infection after childbirth, therapeutic abortion, gastrointestinal surgery, or trauma. Such patients are frequently evaluated for pulmonary embolization, gastrointestinal bleeding, pyelonephritis, and cholecystitis. Unfortunately, such delays in diagnosis increase mortality, and as is the case in most necrotizing soft-tissue infections, by the time local signs and symptoms are apparent, patients are hypotensive, with evidence of organ dysfunction. In contrast, infection is more readily suspected in injection drug users who present with local swelling, pain, and redness at injection sites. This early recognition likely contributes to the lower mortality rate in this group.

Onset of hypotension and tachycardia prompts aggressive initiation of a variety of diagnostic procedures. Among patients with cutaneous evidence of infection, surgical intervention is essential to obtain specimens for Gram stain and culture. CTs and MRIs may reveal swelling of the affected area; however, in postpartum women, an enlarged uterus is not unusual. Gas in the tissues will not be evident unless other organisms, such as *C. perfringens* and *Bacteroides* species, are present. By the time hypotension develops, the complete blood cell count usually reveals a leukemoid reaction and the hematocrit is normal or elevated. Hypotension is persistent and refractory to even massive intravenous fluid administration. Liver function test values, such as bilirubin, alanine aminotransferase level, and alkaline phosphatase level, are usually normal, although the serum albumin decreases precipitously to levels of ≤ 1.0 g/dL. The decrease in the albumin level is clearly related to the diffuse capillary leak syndrome and parallels an increasing hematocrit. At this stage of illness, massive peripheral edema is present, and radiography demonstrates pleural and peritoneal effusions and diffuse pulmonary infiltrates. Patients with such findings develop severe respiratory failure. Persistent hypotension results in elevation of serum creatinine level, increased lactic acid level, a decreasing serum bicarbonate level, and hypoxia, necessitating intubation. Although vasopressors are frequently used in such patients, there is little to suggest they are effective.

Physicians should suspect *C. sordellii* infection in patients who present within 2–7 days after an injury, surgical procedure, drug injection, childbirth, or MIA and who complain of pain, nausea, vomiting, and diarrhea but are afebrile. An increasing WBC count with left shift and evidence of hemoconcentration would strongly suggest *C. sordellii* infection, and a definitive diagnosis should be intensively sought. Imaging studies may reveal the site of infection and thereby facilitate timely surgical intervention for debridement and obtaining diagnostic material. At present, no rapid tests exist to identify *C. sordellii*.

Treatment. There is little, if any, information regarding appropriate treatment for *C. sordellii* infection. In fact, the time between onset of symptoms and death is often so short that little time exists to initiate empirical antimicrobial therapy. Indeed, anaerobic cultures of blood and wound aspirate specimens are time consuming, and many hospital laboratories do not routinely perform antimicrobial susceptibility testing on anaerobes. Antibiotic susceptibility data from older studies suggest that *C. sordellii,* like most clostridia, are susceptible to β-lactams, clindamycin, tetracycline, and chloramphenicol but resistant to aminoglycosides and sulfonamides [83]. Potentially, antibiotics that suppress toxin synthesis (e.g., clindamycin) could be useful adjuncts to therapy, because these agents have been proven to be effective in necrotizing infections due to other toxin-producing, gram-positive organisms [84–86]. Studies to examine the efficacy of bacterial protein synthesis inhibitors in this infection should be undertaken.

Intensive care measures, including administration of intravenous fluids, are required for patients with tachycardia and hypotension. Emergency surgery to remove necrotic tissues is important for diagnosis, source control, and reducing the buildup of toxins. Use of a *C. sordellii* anti-toxin might also be beneficial [15, 16, 21, 26, 28, 34, 37]. Indeed, in experimental studies, antitoxins prevented both cytotoxicity in cell culture systems and lethality in a mouse model of *C. sordellii* toxemia [59, 87, 88]. However, no commercially available antitoxin preparation currently exists for use in humans, but it is worthy of development. Other reported treatments included the administration of steroids, morphine, atropine, and/or vasopressors, all of which have proven to be ineffective once infection was established.

SUMMARY

Renewed interest in *C. sordellii* pathogenesis has followed recent reports of fatal infections associated with MIAs and injection drug use. Indeed, 15 (33%) of all 45 reported cases were associated with these 2 epidemiological groups, and overall, 10 (67%) of 15 patients died. In virtually all cases, the time from onset of symptoms to death was extremely short (2–6 days), and patients invariably developed a profound systemic capillary leak, refractory hypotension, and a marked leukemoid reaction. Diagnosis is confounded by early, nonspecific signs and symptoms and by the absence of fever. Rapid diagnostic tests for *C. sordellii* are largely unavailable but are sorely needed. Mechanisms of pathogenesis of this infection are not clearly defined, but they likely involve potent exotoxins and, possibly, a dysregulated host immune response. The ineffectiveness of currently available treatments is exemplified by a high mortality rate (69%) and extensive morbidity. Additional research is needed to develop molecular techniques to rapidly detect and identify the organism and, potentially, its toxins and to generate novel therapeutic strategies.

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BRIEF REPORT

Fatal Toxic Shock Syndrome Associated with *Clostridium sordellii* after Medical Abortion

Marc Fischer, M.D., M.P.H., Julu Bhatnagar, Ph.D., Jeannette Guarner, M.D.,
Sarah Reagan, M.P.H., Jill K. Hacker, Ph.D., Sharon H. Van Meter, M.D.,
Vadims Poukens, M.D., David B. Whiteman, M.D., Anthony Iton, M.D., J.D., M.P.H.,
Michele Cheung, M.D., M.P.H., David E. Dassey, M.D., M.P.H.,
Wun-Ju Shieh, M.D., Ph.D., and Sherif R. Zaki, M.D., Ph.D.

SUMMARY

Endometritis and toxic shock syndrome associated with *Clostridium sordellii* have previously been reported after childbirth and, in one case, after medical abortion. We describe four deaths due to endometritis and toxic shock syndrome associated with *C. sordellii* that occurred within one week after medically induced abortions. Clinical findings included tachycardia, hypotension, edema, hemoconcentration, profound leukocytosis, and absence of fever. These cases indicate the need for physician awareness of this syndrome and for further study of its association with medical abortion.

From the Centers for Disease Control and Prevention, Atlanta (M.F., J.B., J.G., S.R., W.-J.S., S.R.Z.); the California Emerging Infections Program, Richmond (J.K.H.); the Alameda County Coroners Office (S.H.V.M.) and Health Department (A.I.), Oakland, Calif.; the Department of the Coroner (V.P., D.B.W.) and the Department of Health Services (D.E.D.), Los Angeles; and the Orange County Health Care Agency, Santa Clara, Calif. (M.C.). Address reprint requests to Dr. Fischer at the Centers for Disease Control and Prevention, P.O. Box 2087, Mailstop P-02, Fort Collins, CO 80522, or at mfischer@cdc.gov.

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CLOSTRIDIUM SORDELLII IS A GRAM-POSITIVE ANAEROBIC BACILLUS THAT has been reported as a cause of infection in the female genital tract and fatal toxic shock syndrome. Of 10 cases identified in the literature, 8 occurred after delivery of live-born infants,[1-6] 1 occurred after a medical abortion,[7] and 1 was not associated with pregnancy.[8] We report four additional deaths due to *C. sordellii* toxic shock syndrome that occurred among previously healthy women after abortions that were medically induced with 200 mg of oral mifepristone and 800 μg of vaginal misoprostol.

CASE REPORTS

PATIENT 1

Patient 1 was a previously healthy 18-year-old woman who underwent a medically induced abortion at 47 days of gestation by means of 200 mg of oral mifepristone followed by 800 μg of vaginal misoprostol. Four days after receiving mifepristone, the patient presented to an emergency department with reports of abdominal cramping and dysuria. She had taken acetaminophen with codeine after the abortion. On physical examination, she was afebrile with normal vital signs and no abdominal tenderness. Pelvic examination revealed no uterine tenderness or adnexal mass. No laboratory studies or cultures were performed. She received hydromorphone and promethazine and was discharged taking acetaminophen and codeine.

The patient returned three days later and reported nausea, vomiting, and weakness. On admission, she was afebrile (temperature, 36.3°C), tachycardic (heart rate, 147 beats per minute), and hypotensive (blood pressure, 78/53 mm Hg) and had dry mucous membranes but unremarkable findings on abdominal and pelvic examinations. Laboratory studies showed an elevated white-cell count of 45,600 cells per microliter, a platelet count of 387,000 cells per microliter, and a hematocrit of 52 percent. Creatinine and liver-function studies were normal. Blood cultures obtained before antibacterial therapy were later found to be negative for bacteria; vaginal cultures grew gardnerella species. Ultrasonographic examination of the pelvis showed a residual gestational sac in the uterus and a large amount of free peritoneal fluid. A chest radiograph showed bilateral interstitial infiltrates.

Initial treatment included supplemental oxygen, intravenous fluids, and antibacterial therapy with vancomycin and piperacillin–tazobactam. During the next few hours, the patient had respiratory distress and hypotension requiring mechanical ventilation and vasopressor support. Initial arterial blood gas measurements revealed severe metabolic acidosis, with a pH of 7.15, a partial pressure of carbon dioxide of 36 mm Hg, and a bicarbonate concentration of 13 mmol per liter. Within seven hours after admission, the white-cell count increased to 107,000 cells per microliter, with a hematocrit of 58 percent and a platelet count of 158,000 cells per microliter. Urine output and the serum albumin concentration decreased markedly, but concentrations of hepatic enzymes, bilirubin, and creatinine remained normal. Refractory bradycardia, hypotension, and hypoxemia developed, and the patient died approximately 10 hours after admission.

PATIENT 2

Patient 2 was a previously healthy 21-year-old woman who underwent a medically induced abortion at 43 days of gestation by means of 200 mg of oral mifepristone followed by 800 μg of vaginal misoprostol. Five days after receiving mifepristone, she reported abdominal pain and vomiting. The following morning she became unresponsive. When paramedics arrived, she had no spontaneous respirations or cardiac activity. She was transported to a local emergency department while receiving ongoing cardiopulmonary resuscitation. Physical examination showed a rectal temperature of 38.9°C, fixed and dilated pupils, and mild abdominal distention. The serum glucose concentration was 108 mg per deciliter. Toxicologic evaluation was negative. No other laboratory studies or cultures were performed. The patient was intubated and received intravenous fluids, epinephrine, and atropine. Resuscitation efforts were discontinued 40 minutes after her arrival at the emergency department.

PATIENT 3

Patient 3 was a previously healthy 22-year-old woman who underwent a medically induced abortion at 53 days of gestation by means of 200 mg of oral mifepristone followed by 800 μg of vaginal misoprostol. Five days after receiving mifepristone, she presented to a local emergency department reporting nausea, vomiting, diarrhea, and severe abdominal pain. The patient was afebrile (temperature, 36.2°C), with a heart rate of 104 beats per minute and blood pressure of 115/76 mm Hg. Physical examination was unremarkable except for moderate abdominal tenderness. Laboratory findings included a white-cell count of 21,800 cells per microliter, a platelet count of 256,000 cells per microliter, and a hematocrit of 40 percent. Ultrasonographic examination of the pelvis showed a left adnexal mass and fluid in the cul-de-sac. The patient received intravenous fluids, promethazine, and morphine and was admitted to the hospital to rule out an ectopic pregnancy.

The following day, persistent tachycardia (heart rate, 130 to 140 beats per minute), hypotension (blood pressure, 80/40 mm Hg), lethargy, decreased urine output, and diffuse abdominal tenderness developed, and the patient was transferred to the intensive care unit. Laboratory findings included a white-cell count of 120,200 cells per microliter, a platelet count of 91,000 cells per microliter, a hematocrit of 45 percent, a creatinine concentration of 1.9 mg per deciliter (168 μmol per liter), an albumin concentration of 1.0 g per deciliter, and a prothrombin time of 18.3 seconds with normal levels of aminotransferases and bilirubin. Arterial blood gas measurements showed severe metabolic acidosis, with a pH of 7.15, a partial pressure of carbon dioxide of 29 mm Hg, and a bicarbonate concentration of 10 mmol per liter. Antibacterial therapy was initiated with piperacillin–tazobactam and metronidazole; blood cultures obtained before antibacterial therapy were subsequently found to be negative for bacteria. Within three hours after being transferred to the intensive care unit, the patient had a cardiopulmonary arrest requiring mechanical ventilation and vasopressor support. Emergency laparotomy showed generalized edema of the abdominal and pelvic organs and 1000 ml of serous peritoneal fluid. Gram's stain and aerobic and anaerobic cultures of peritoneal fluid obtained intraoperatively were negative for bacteria. The patient died during the surgical procedure, approximately 23 hours after her initial presentation to the hospital.

PATIENT 4

Patient 4 was a previously healthy 34-year-old woman who underwent a medically induced abortion at

45 days of gestation by means of 200 mg of oral mifepristone followed by 800 μg of vaginal misoprostol. Four days after receiving mifepristone, she presented to a local emergency department reporting nausea, vomiting, and severe abdominal pain. She had taken ondansetron and acetaminophen with hydrocodone after the abortion. The patient was afebrile (temperature, 36.3°C), with a heart rate of 89 beats per minute and blood pressure of 99/63 mm Hg. Physical examination was unremarkable except for moderate abdominal tenderness. Laboratory findings included a white-cell count of 55,400 cells per microliter, a platelet count of 149,000 cells per microliter, and a hematocrit of 59 percent. Ultrasonographic examination of the pelvis showed an empty uterus. Initial treatment included intravenous fluids, ondansetron, and hydromorphone.

After the patient received 2 liters of normal saline, a repeated blood count showed a white-cell count of 87,600 cells per microliter, a platelet count of 63,000 cells per microliter, and a hematocrit of 61 percent. Serum chemical analyses including liver-function tests were unremarkable. Aerobic and anaerobic blood cultures and a urine culture were obtained but were subsequently negative for bacteria; antibacterial therapy was initiated with piperacillin–tazobactam and metronidazole. A chest radiograph was normal. Computed tomography of the abdomen showed only a moderate volume of free fluid. Although the patient received 5 liters of intravenous fluids, worsening tachycardia and hypotension with minimal urine output developed. Arterial blood gas measurements showed severe metabolic acidosis, with a pH of 7.07, a partial pressure of carbon dioxide of 10 mm Hg, and a bicarbonate concentration of 3 mmol per liter. Further therapy included sodium bicarbonate and vasopressor support, but refractory hypotension developed and the patient died approximately 12 hours after presentation.

METHODS

We reviewed medical and autopsy records for each patient. Formalin-fixed tissues were evaluated at the Centers for Disease Control and Prevention. Immunohistochemical assays were performed for clostridium species, *Staphylococcus aureus*, group A streptococcus, and neisseria species by means of a two-step indirect staining technique with immunoalkaline phosphatase. The polyclonal anti-clostridium antibody used in the immunohistochemical assay cross-reacts with multiple clostridium species.[9] DNA was extracted from formalin-fixed uterine tissue with the use of the QIAamp DNA Mini Kit (Qiagen) and was evaluated with broad-range and *C. sordellii*–specific polymerase-chain-reaction (PCR) assays targeting the 16S ribosomal RNA (rRNA) gene and with PCR assays targeting the *C. sordellii* cytotoxin L and phospholipase C genes (Table 1).[10-14] Amplified PCR products were directly sequenced and, with the use of the Basic Local

Table 1. **Primers Used in PCR Assays on Formalin-Fixed Tissues.**

Gene Target	Primer	Sequence (5′ to 3′)	Product Size (bp)	Reference
16S rRNA*	F8	AGT TTG ATC CTG GCT CAG	330	Daly et al.[10] and Stackebrandt and Charfreitag[11]
	357R	CTG CTG CCT CCC GTA		
16S rRNA†	C1SOR-F	TCG AGC GAC CTT CGG	944	Kikuchi et al.[12]
	C1SOR-R	CAC CAC CTG TCA CCA T		
CytL‡	CLS-F1	ATG AAC TTA GTT AAC AAA GCC CAA	250	—§
	CLS-R1	AAT ACT TCC ATA GTT AGA TAT TCT TTA		
Csp¶	CLS-F2	TAA AGA TGC AGT AGC TAA TAA GGA TTT	223	—‖
	CLS-R2	TTC CTG AAA TTT GAT CTT CTG AAA CC		

* A broad-range PCR assay was used to target the 16S rRNA gene.

† A *C. sordellii*–specific PCR assay was used to target the 16S rRNA gene.

‡ CytL denotes the cytotoxin L–encoding gene of *C. sordellii*.

§ Primers were designed for this investigation from the published sequence of *C. sordellii* (GenBank accession number X82638).[13]

¶ Csp denotes the phospholipase C gene of *C. sordellii*.

‖ Primers were designed for this investigation from the published sequence of *C. sordellii* (GenBank accession number AB061868).[14]

Alignment Search Tool (BLAST), compared with sequences available in the GenBank database.

The National Center for Infectious Diseases determined that this investigation was defined as a public health response. Approval of the institutional review boards and consent of the next of kin were not required to evaluate and publish these case reports.

RESULTS

Autopsy of Patient 1 revealed marked pleural, pericardial, and peritoneal effusions. Histopathological examination of the uterus showed inflammation of endometrium and myometrium, multiple small abscesses, necrosis, and hemorrhage (Fig. 1A). There was no retained fetal or placental tissue. Other organs were unremarkable. Mixed bacteria, including numerous gram-positive bacilli, were seen in the endometrium (Fig. 1B). Postmortem cultures were not performed. Immunohistochemical testing of uterine tissue was negative for *S. aureus*, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed extensive staining of bacilli and granular antigens associated with areas of inflammation in the endometrium and myometrium (Fig. 1C). Clostridial antigens were noted in blood vessels of the uterus (Fig. 1D) but were not observed in brain, heart, lung, liver, kidney, or adrenal tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 98 percent identity with *C. sordellii*. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed

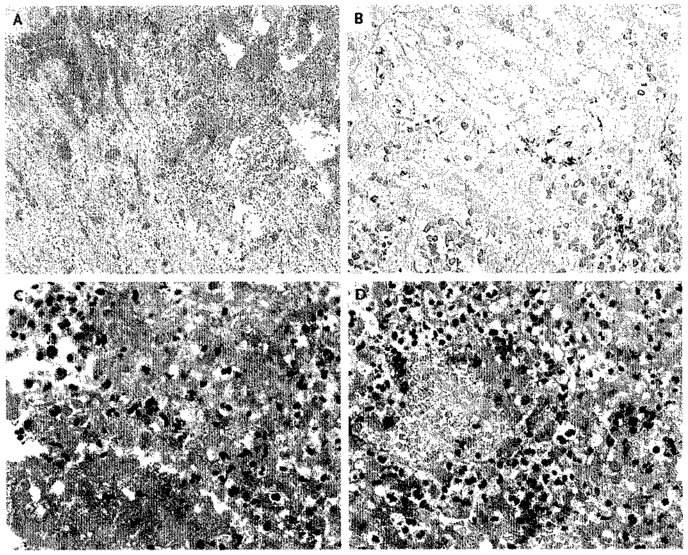

Figure 1. **Photomicrographs of the Uterine Tissue of Patient 1.**

Panel A shows hemorrhage, inflammation, and necrosis of the endometrium (hematoxylin and eosin). Abundant gram-positive bacilli were observed in the necrotic endometrial tissue (Panel B, Gram's stain). Clostridial antigens (red staining) were seen inside inflammatory cells present in the necrotic endometrial tissue (Panel C, immunohistochemical assay with the use of polyclonal anti–clostridium species antibody) and inside myometrial blood vessels closest to the necrotic endometrium (Panel D, immunohistochemical assay with the use of polyclonal anti–clostridium species antibody).

99 percent and 97 percent identity with *C. sordellii*, respectively.

The body of Patient 2 was initially embalmed, and an autopsy was performed one week after death. Histopathological examination of the uterus showed severe inflammation of endometrium and myometrium, necrosis, and hemorrhage with retained necrotic decidual tissue. Mixed bacteria, predominantly gram-positive bacilli, were seen in the endometrium. Immunohistochemical testing of uterine tissue was negative for *S. aureus*, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed extensive staining of bacilli and granular antigens associated with areas of inflammation in the endometrium and myometrium. Clostridial antigens were not observed in brain, heart, lung, liver, kidney, or adrenal tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 98 percent identity with *C. sordellii*. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 98 percent and 97 percent identity with *C. sordellii*, respectively.

Autopsy of Patient 3 revealed pleural and peritoneal effusions. Histopathological examination of the uterus showed extensive inflammation, abscess formation, edema, necrosis, and hemorrhage. There was no retained fetal or placental tissue and no evidence of ectopic pregnancy. Mixed bacteria, including numerous gram-positive bacilli, were seen in the endometrium. Postmortem cultures were not obtained. Immunohistochemical testing of uterine tissue was negative for group A streptococcus and neisseria species but showed *S. aureus* antigens on the endometrial surface. Clostridium immunohistochemical analysis showed extensive staining of bacilli and granular antigens associated with areas of inflammation throughout the endometrium and myometrium. Clostridial antigens were not observed in heart, lung, liver, or kidney tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 97 percent identity with *C. sordellii*. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 99 percent and 98 percent identity with *C. sordellii*, respectively.

Autopsy of Patient 4 revealed pleural, pericardial, and peritoneal effusions. Histopathological examination of the uterus showed severe inflammation of endometrium and myometrium, necrosis, and hemorrhage, with extensive inflammation and edema. Abundant gram-positive bacilli were seen in the endometrium. Postmortem cultures of the endometrium grew *Escherichia coli* and an anaerobic gram-positive bacillus that was discarded before further identification. Immunohistochemical testing of uterine tissue was negative for *S. aureus*, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed staining of bacilli and abundant granular antigens associated with areas of inflammation throughout the endometrium and myometrium. Clostridial antigens were not observed in heart, lung, liver, spleen, pancreas, kidney, adrenal, or ovarian tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 98 percent identity with *C. sordellii*. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 98 percent and 97 percent identity with *C. sordellii*, respectively.

DISCUSSION

We describe four deaths associated with *C. sordellii* endometritis and toxic shock syndrome that occurred within one week after medically induced abortions. The clinical and pathological findings in these cases are similar to those in 10 other cases of *C. sordellii* infection of the genital tract reported in the literature[1-8] (Table 2). Of the 10 previous cases that we identified, all occurred in previously healthy young women, and 9 occurred within one week after delivery (8 women) or after abortion (1 woman). Notable clinical features included absence of fever and rash, dramatic leukemoid reaction, capillary leak and fluid sequestration with associated hemoconcentration, refractory tachycardia and hypotension, and marked edema of infected tissues without gas production or extensive myonecrosis. All the cases had a fulminant course and fatal outcome. Eight of the previously reported cases had evidence of a polymicrobial infection. Although infections of the female genital tract often include mixed bacteria, the role of other organisms in toxic shock syndrome associated with *C. sordellii* is unclear.

C. sordellii is an infrequent human pathogen but has been reported as a cause of pneumonia, endocarditis, arthritis, peritonitis, and myonecrosis.[1,15-17] *C. sordellii* bacteremia and sepsis occur rarely, primarily among patients with serious underlying conditions.[18] Fulminant toxic shock syndrome among previously healthy persons has been described in only a small proportion of cases of *C. sordellii* infection, most often those associated

Table 2. **Characteristics of Women with *C. sordellii* Infections of the Genital Tract and Toxic Shock Syndrome.**

Characteristic	Currently Reported Patients (N=4)	Previously Reported Patients (N=10)*
Age — yr		
Median	22	25
Range	18–34	23–40
Fatal outcome — no. (%)	4 (100)	10 (100)
Underlying medical conditions — no.	0	0
Preceding event — no. (%)		
Childbirth	0	8 (80)†
Medical abortion	4 (100)	1 (10)
None	0	1 (10)
Time course (days)		
From event to onset of symptoms		
Median	5	3
Range	4–5	2–5
From hospitalization to death		
Median	0	0
Range	0–1	0–3
Clinical signs and symptoms — no. (%)		
Temperature >38.0°C	1 (25)	1 (10)
Tachycardia	4 (100)	9 (90)
Hypotension	4 (100)	10 (100)
Pleural or peritoneal effusions	3 (75)	8 (80)
Vomiting or diarrhea	4 (100)	5 (50)
Abdominal pain	4 (100)	5 (50)
Rash	0	1 (10)‡
Laboratory findings — no. (%)		
White-cell count >50,000 cells/microliter	3 (75)	8 (80)
Hematocrit ≥50%	3 (75)	7 (70)
Microbiologic findings — no. (%)		
Evidence of polymicrobial infection	4 (100)	8 (80)
C. sordellii isolated from blood	0	1 (10)
Focus of infection — no. (%)		
Uterus	4 (100)	7 (70)
Site of episiotomy	0	3 (30)
Pathological findings at the focus of infection — no. (%)		
Edema	3 (75)	10 (100)
Necrosis	4 (100)	8 (80)
Acute inflammation	4 (100)	8 (80)
Hemorrhage	3 (75)	2 (20)
Gas	0	0

* This information has been reported elsewhere.[1-8]

† Six deliveries were vaginal, and two were by cesarean section.[1-6]

‡ This rash was described as vesicles on the perineum that enlarged to bullous lesions and spread to the legs and trunk.[6]

with gynecologic infections and neonatal omphalitis.[1-8,17] The distinctive clinical manifestations of *C. sordellii* toxic shock syndrome result from the production of specific exotoxins, as do those of other illnesses caused by clostridium species.[15,16,19] In animal models, *C. sordellii* lethal toxin causes findings similar to those described in these human cases.[15,19] Lethal toxin is expressed variably by different *C. sordellii* strains,[20] and its cytopathic effects are markedly enhanced by a low pH.[21]

Although *C. sordellii* has rarely been identified in the genital tract, other clostridium species colonize the vagina in 4 percent to 18 percent of healthy women and commonly are associated with postpartum endometritis and septic abortion.[22-25] Vaginal flora vary with age, sexual activity, menstrual cycle, pregnancy, medications, and surgery,[22] and the apparent association between *C. sordellii* toxic shock syndrome and gynecologic infections may be attributed to a rare confluence of events. Pregnancy, childbirth, or abortion may predispose a small number of women to acquire *C. sordellii* in the vaginal tract, with dilatation of the cervix allowing for ascending infection of necrotic decidual tissue. Furthermore, the acidic pH of the vaginal tract may enhance the cytopathic effects of *C. sordellii* lethal toxin and further potentiate systemic illness.

The fastidious anaerobic growth, variable staining characteristics, and complex biochemical profiles of clostridium species make them difficult to isolate and identify, and additional cases of *C. sordellii* infection of the genital tract in which the organism was not cultured, speciated, or reported probably exist.[26,27] In the four cases reported here, evidence of *C. sordellii* infection was established with the use of anti–clostridium species immunohistochemical assay and both organism-specific and broad-range PCR assays performed on fixed uterine tissue. Identification of additional cases and application of anaerobic culture techniques or new diagnostic approaches are needed to define the true burden of *C. sordellii* in gynecologic infections.

There are limited data regarding the optimal therapy for *C. sordellii* toxic shock syndrome. As with other severe histotoxic clostridial infections, aggressive surgical wound débridement, removal of infected organs (e.g., by means of hysterectomy), and antibacterial agents with good anaerobic activity are logical first steps to decrease the bacterial load and minimize further production of toxins.[1,23] In vitro susceptibility testing on 24 *C. sordellii* strains showed low minimal inhibitory concentrations for penicillin, ampicillin, erythromycin, rifampin, tetracycline, cefoxitin, clindamycin, and metronidazole[28]; antibiotics that interfere with bacterial protein synthesis (such as clindamycin) may have additional benefit. However, débridement, surgery, and antibacterial therapy will not mitigate the effects of preformed toxin. There are no clinical data on the use of immunoglobulin or anti–lethal toxin antibodies for treatment of *C. sordellii* infections.[16,17]

These cases demonstrate that serious infection can occur after medically induced abortion, much as it can occur after childbirth, spontaneous abortion, and surgical abortion. However, available data suggest that the risk of such infection is low.[29,30] In 2000, 600 mg of oral mifepristone plus 400 µg of oral misoprostol was approved for use in the United States to medically terminate a pregnancy of up to seven weeks' gestation. As of July 2005, five deaths that occurred after medically induced abortions had been reported to the Food and Drug Administration (FDA). These include the four patients described here and one patient whose death was attributed to a ruptured ectopic pregnancy.[31] Since its approval, there have been an estimated 460,000 uses of mifepristone plus misoprostol in the United States.[32] It is not clear how many women this estimate represents. The 460,000 uses may include the regimen approved by the FDA or other dosages, such as 200 mg of oral mifepristone followed by 800 µg of intravaginal misoprostol.

There are no available incidence data for pregnancy-related *C. sordellii* infections or toxic shock syndrome. However, overall rates of infection-related deaths after pregnancy are well described. From 1991 to 1999, 259 maternal deaths due to infection were identified after 35,701,875 live births in the United States.[33,34] From 1981 to 1991, 37 infection-related maternal deaths were associated with 9,279,100 spontaneous abortions at less than 20 weeks' gestation.[35] From 1988 to 1997, 25 maternal deaths attributed to infection were reported after 13,161,608 surgical abortions at any point in gestation.[36] These data must be interpreted with caution, however, because each estimate was obtained with the use of different methods and over different periods. Furthermore, the risk of maternal death after surgical abortion increases with gestational age, and there are no published estimates for the rate of maternal death after surgical abortion performed during the first trimester.

In 2001, one additional death due to *C. sordellii* infection after medical abortion was reported in Canada.[7] Although all four cases reported in the present study occurred in California, there were no epidemiologic links identified between the patients, and the medications received were from different lots. Some researchers have speculated about the mechanisms by which oral mifepristone or intravaginal misoprostol could potentiate *C. sordellii* infection or toxic shock syndrome.[37] However, additional data are needed to evaluate further the possible association between medical abortion and *C. sordellii* infections, define the spectrum of illness, and identify risk factors for toxic shock syndrome.

The side effects of misoprostol (e.g., vomiting, diarrhea, and abdominal cramping) may be similar to the initial symptoms of toxic shock syndrome associated with *C. sordellii*.[38] To improve diagnosis and therapy, clinicians should be aware of the distinctive features of this potentially fatal entity, including tachycardia, hypotension, edema, hemoconcentration, profound leukocytosis, and absence of fever. Health care providers should report to their state or local health department any cases of toxic shock syndrome occurring after an abortion or associated with pregnancy.

The views expressed are those of the authors and do not necessarily represent the views of the Department of Health and Human Services.

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Medical Management of Abortion

Over the past two decades, medical methods of abortion have been developed throughout the world and are now used in the United States. Medical abortion, which involves the use of medications to induce an abortion rather than a surgical abortion, is an option for women who wish to terminate a pregnancy up to 63 days of gestation (calculated from the first day of the last menstrual period). Medical abortions currently account for 6% of all abortions in the United States (1). The purpose of this document is to present evidence of the effectiveness, benefits, and risks of medical abortion and provide a framework for the evaluation and counseling of women who are considering medical abortion.

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Mitchell D. Creinin, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Background

Medications Currently Used in Medical Abortion

Mifepristone

Mifepristone (RU-486), a derivative of norethindrone, binds to the progesterone receptor with an affinity greater than progesterone but does not activate the receptor, thereby acting as an antiprogestin (2). Mifepristone's known actions on a pregnant uterus include necrotizing the decidua, softening the cervix, and increasing both uterine contractility and prostaglandin sensitivity (3, 4). Human studies have suggested that uterine contractility does not increase until 24–36 hours after mifepristone administration (4). At this point, the myometrium is five times more sensitive to the stimulatory effects of exogenous prostaglandins (4).

Administration of mifepristone followed by a prostaglandin analogue, usually misoprostol, is the most commonly used medical abortion regimen throughout the world. As a progesterone receptor antagonist, mifepristone also has several other potential medical applications, including emergency contraception, cervical ripening for labor induction, and treatment of conditions such as symptomatic leiomyomata uteri, endometriosis, Cushing's syndrome, breast cancer, and glaucoma.

Misoprostol

Misoprostol is an inexpensive prostaglandin analogue in a tablet form that is stable at room temperature. Misoprostol is used clinically for prevention of gastric ulcers in individuals taking antiinflammatory drugs on a long-term basis, for abortion, and for labor induction. Pharmacokinetic evaluation of oral and vaginal administration of misoprostol demonstrates that oral misoprostol is absorbed more rapidly, resulting in a higher peak serum level (5, 6), but vaginal administration results in greater uterine contractility. Recent evaluations of sublingual administration show higher peak serum concentrations (7, 8), which may result in more unnecessary side effects (7). Further study of buccal administration may be warranted because its pharmacokinetic profile appears to be similar to vaginal administration (7).

Other Agents

Methotrexate is used less often today for medical abortion because of the greater availability of mifepristone. Methotrexate blocks dihydrofolate reductase, an enzyme involved in producing thymidine during DNA synthesis. Methotrexate exerts its action primarily on the cytotrophoblast rather than the developing embryo. Methotrexate has been used for more than 40 years to treat neoplastic diseases, rheumatoid arthritis, and psoriasis; other medical applications include treatment of systemic lupus erythematosus, dermatomyositis, severe asthma, Crohn's disease, and extrauterine pregnancy.

Tamoxifen has been used in combination with misoprostol in some studies of early abortion. However, randomized trials have demonstrated no benefit of using a tamoxifen–misoprostol regimen compared with a methotrexate–misoprostol regimen (9) or misoprostol alone (10).

Mifepristone Regimens

Protocol Approved by the U.S. Food and Drug Administration

Mifepristone regimens vary according to dosage, timing, and route of administration (see Table 1). The U.S. Food and Drug Administration (FDA) approved the protocol of mifepristone, 600 mg orally, followed approximately 48 hours later by misoprostol, 400 μg orally. This is safe and effective for medical abortion through 49 days of gestation (calculated from the first day of the last menstrual period [LMP]). A follow-up evaluation is scheduled approximately 14 days after administration of mifepristone. At that time, if clinical history and physical examination do not confirm expulsion, ultrasonography is performed. If a gestational sac is seen, aspiration is typically performed.

Efficacy with this regimen is approximately 92% in women with pregnancies up to 49 days of gestation (11, 12). Complete abortion rates are higher with earlier gestations: approximately 96–98% for pregnancies up to 42 days of gestation (13, 14), 91–95% from 43 to 49 days of gestation (13, 14), and less than 85% beyond 49 days of gestation (11, 13, 14).

Alternative Regimens

Other evidence-based medical abortion regimens have been developed in an effort to reduce side effects and to make medical abortion less expensive, safer, and more rapid. Regimens using 200-mg doses of mifepristone orally have efficacy rates comparable to the FDA-approved regimen (12, 15) at one third of the cost. Additionally, increasing the misoprostol dose to 800 μg and administering the medication vaginally decreases the time to expulsion (16), results in fewer side effects (16, 17), and improves complete abortion rates when compared with oral administration of a 400-μg dose of misoprostol (16, 18–20). Multiple large studies in the United States have demonstrated that a patient can safely and effectively self-administer the misoprostol (orally or vaginally) in her home (18, 19, 21–27).

Investigations also have demonstrated the flexibility in timing between the two medications. One study demonstrated that 800 μg of misoprostol may be administered either 24, 48, or 72 hours after 200 mg of mifepristone with equal efficacy in pregnancies up to 56 days of gestation (23); a follow-up study using a regimen with a 24-hour interval between medications yielded similar results in pregnancies up to 63 days of gestation (24). Moreover, the results of a randomized multicenter study indicated that 800 μg of misoprostol administered vaginally 6–8 hours after 200 mg of mifepristone resulted in significantly fewer side effects (and no decrease in efficacy) than regimens using a 24-hour interval (27).

Compared with the FDA-approved regimen, mifepristone–misoprostol regimens using mifepristone, 200 mg orally, and misoprostol, 800 μg vaginally, are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP.

Nonmifepristone Regimens

Methotrexate and Misoprostol

The combination of methotrexate and misoprostol is an alternative early medical abortion regimen. Among

Table 1. Comparison of Common Medical Abortion Regimens

Common Regimens	Overall Success Rate (%)	Advantages and Disadvantages	Gestational Age
Mifepristone, 600 mg orally + misoprostol, 400 μg orally (FDA-approved regimen)	92[a]	Must remain in office or clinic 4 hours after administration	Up to 49 days
Mifepristone, 200 mg orally + misoprostol, 800 μg vaginally (alternative evidence-based regimen)	95–99[b–f]	Compared with FDA-approved regimen: • More effective • Less time to expulsion • Fewer side effects • Requires vaginal administration of a medication	Up to 63 days
Methotrexate, 50 mg/m^2 IM or 50 mg vaginally, + misoprostol, 800 μg vaginally 3–7 days later	92–96[g–i]	Compared with mifepristone–misoprostol regimen: • Takes longer for expulsion in 20–30% of women • Readily available medications • Low drug cost	Up to 49 days
Misoprostol only, 800 μg vaginally repeated for up to three doses	88[j]	• Requires complicated dosing regimens • Significantly higher incidence of side effects than other regimens • Low drug cost	Up to 56 days

Abbreviations: FDA, U.S. Food and Drug Administration; IM, intramuscularly

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women with pregnancies up to 49 days of gestation, this regimen results in a complete abortion rate of 92–96%. Between 50 days and 56 days of gestation, however, efficacy decreases to 82% (28). Although overall efficacy is equal to the standard regimen of mifepristone–misoprostol, approximately 15–25% of women using methotrexate regimens may wait up to 4 weeks for complete abortion to occur (25, 29, 30).

Methotrexate is most commonly administered intramuscularly at a dose based on body surface area (50 mg/m^2), the same dose used for the management of ectopic pregnancy (31). However, regimens using 50 mg of methotrexate orally appear to be as effective as those using methotrexate, 50 mg/m^2 intramuscularly (29, 32, 33). Misoprostol (800 μg) is administered by the woman 3–7 days later at home. A follow-up examination is performed approximately 1 week after methotrexate administration; a vaginal ultrasound examination is performed to confirm passage of the gestational sac. If abortion has not occurred, the misoprostol dose is repeated. Further follow-up for women requiring a second dose of misoprostol is performed in 4 weeks unless embryonic cardiac activity is still visible on ultrasound examination, in which case patients return in 1 week. If gestational cardiac activity is present 2 weeks after initiating treatment or expulsion has not occurred by the 4-week follow-up visit, aspiration is performed.

Misoprostol Alone

Misoprostol, 800 μg vaginally, when moistened with water, can result in complete abortion rates of 90% in women with pregnancies up to 56 days of gestation

(10, 34–38). Studies with nonmoistened vaginal misoprostol demonstrated lower rates of 50–67% (39–41). Studies showing that misoprostol alone is effective for abortion often involve complex dosing regimens or require clinician application of the tablets. Additionally, this treatment results in significantly higher rates of side effects (nausea, vomiting, diarrhea, and fever and chills) than those using misoprostol after pretreatment with either mifepristone or methotrexate (10, 34–37). Recent trials with sublingual misoprostol in repeated doses do not appear to improve outcome over vaginal misoprostol and may cause even more side effects (38, 42).

A recent randomized, double-blind trial in women with pregnancies up to 56 days of gestation compared a misoprostol-only regimen (800 μg vaginally) with a regimen of 200 mg of mifepristone orally followed 48 hours later by 800 μg of misoprostol vaginally (43). In both groups, misoprostol was repeated every 24 hours for up to three doses. Complete abortion rates for each regimen were 88.0% and 95.7%, respectively ($P<.05$). The women who received mifepristone aborted much more quickly and required fewer doses of misoprostol compared with women who received misoprostol alone.

Mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 μg of misoprostol vaginally generally are preferred to regimens using methotrexate and misoprostol or misoprostol only for medical abortion.

Counseling Patients

Medical Versus Surgical Abortion

Patient counseling must first include discussion of pregnancy options to be sure that a woman is certain about her decision to have an abortion. If she is uncertain, the decision about abortion technique must be delayed until she has reached a firm decision, even if the delay means that she will be unable to choose a medical option. It is important to respect the patient's autonomy and to separate the decision to terminate the pregnancy from the decision about the method to be used.

After a woman has considered her options and has decided to have an abortion, the method must be selected. Most women seeking early abortion will be eligible for both medical and surgical methods. Medical abortion should be considered a medically acceptable alternative to surgical abortion in selected, carefully counseled, and informed women. The general advantages and disadvantages of each approach (Table 2) should be explained early in the counseling process because most women will have a clear preference (44, 45). Even among women who think they are unsure, most will have some preference after counseling (44).

Table 2. Features of Medical and Surgical Abortion

Medical Abortion	Surgical Abortion
• Usually avoids invasive procedure	• Involves invasive procedure
• Usually avoids anesthesia	• Allows use of sedation if desired
• Requires two or more visits	• Usually requires one visit
• Days to weeks to complete	• Complete in a predictable period of time
• Available during early pregnancy	• Available during early pregnancy
• High success rate (~95%)	• High success rate (99%)
• Bleeding moderate to heavy for short time	• Bleeding commonly perceived as light
• Requires follow-up to ensure completion of abortion	• Does not require follow-up in all cases
• Patient participation throughout a multiple-step process	• Patient participation in a single-step process

Adapted from Breitbart V. Counseling for medical abortion. Am J Obstet Gynecol 2000;183:S26–33.

Counseling and Symptom Management

Some degree of bleeding and uterine cramping are necessary for the medical abortion process to occur. Other potential side effects of medical abortion include nausea, vomiting, diarrhea, warmth or chills, headache, dizziness, and fatigue (Table 3). Counseling should emphasize that bleeding may be much heavier than menses, potentially with severe cramping. The woman should understand how much bleeding is considered too much. An easy reference for the patient to use is soaking of two pads per hour for 2 hours in a row (46). This is not necessarily a point at which intervention is needed but a time when the woman should call the health care provider. Whether or not it is imperative for the patient to seek emergency care depends on how she is feeling, her baseline hemoglobin, whether the bleeding seems to be slowing, and how far she is from an emergency treatment facility.

Pain management is especially important for the woman aborting at home. She should be sent home with appropriate instructions for analgesia with over-the-counter medications, as well as with prescriptions for oral narcotics to use if needed.

The incidence of each symptom will depend on the regimen used, the dose and route of administration of the prostaglandin analogue, and gestational age. Gastrointestinal side effects are less common when dry misoprostol is administered vaginally compared with regimens that use oral misoprostol or moistened vaginal misoprostol. Oral ulcers with methotrexate use, although rare, have been reported in the literature.

Table 3. Incidence of Side Effects in Selected North American Trials of Medical Abortion Regimens*

	Incidence of Side Effects (%)											
	Nausea		Vomiting		Diarrhea		Headache		Dizziness		Thermoregulatory[†]	
Trial	Mife	Miso	Mife	Miso	Mife	Miso	Mife	Miso	Mife	Miso	Mife	Miso
Schaff et al (1997)[‡]	36	36	14	14	8	22	18	19	22	37	20	37
Schaff et al (1999)[§]	45	43	13	26	11	23	14	13	15	28	14	32
Wiebe et al (2002)[‖]	45	39	13	15	5	16	19	29	NR	NR	NR	23
Creinin (2004)[¶]	20	44	5	23	1	27	10	37	12	35	9	56
Creinin (2004)[#]	39	52	14	30	7	25	20	37	20	37	19	53

Abbreviations: Mife, mifepristone; Miso, misoprostol; NR, not reported

*Studies are included only if the incidences of side effects were differentiated between the medications.

[†] Fever, warmth, hot flashes, or chills

[‡] Mifepristone, 600 mg, followed by misoprostol, 800 μg vaginally, 36–48 hours later. (Schaff EA, Stadalius LS, Eisinger SH, Franks P. Vaginal misoprostol administered at home after mifepristone (RU486) for abortion. J Fam Pract 1997;44:353–60.)

[§] Mifepristone, 200 mg, followed by misoprostol, 800 μg vaginally, 48 hours later. (Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. Contraception 1999;59:1–6.)

[‖] Mifepristone, 600 mg, followed by misoprostol, 400 μg orally, 36–48 hours later. (Wiebe E, Dunn S, Guilbert E, Jacot F, Lugtig L. Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. Obstet Gynecol 2002;99:813–9.)

[¶] Mifepristone, 200 mg, followed by misoprostol, 800 μg vaginally, 6–8 hours later (first row). (Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004;103:851–9.)

[#] Mifepristone, 200 mg, followed by misoprostol, 800 μg vaginally, 23–25 hours later (second row). (Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004;103: 851–9.)

Need for Follow-up Dilation and Curettage

A failed medical abortion is defined as the presence of gestational cardiac activity on vaginal ultrasonography 2 weeks after the initiation of treatment. No studies have assessed the efficacy of additional doses of mifepristone, methotrexate, or misoprostol after a medical abortion failure. Continuing pregnancies, which should be terminated by surgical evacuation, are typically reported in less than 1% of women who begin treatment at 49 days of gestation or less regardless of regimen.

Intervention guidelines vary for women who have a persistent gestational sac seen on ultrasonography without evidence of embryonic cardiac activity or continuing development. Typically, protocols used in mifepristone studies define a retained sac 2 weeks after the administration of mifepristone as an indication for suction evacuation. However, medical abortion studies using methotrexate and misoprostol demonstrate that intervention for a nonviable pregnancy is unnecessary and that expulsion will occur, on average, between 22 and 29 days after the methotrexate is administered (28, 29, 40, 47, 48). With this understanding, the mifepristone studies performed in the United States over the past 6 years have allowed approximately 36 days to elapse after mifepristone administration before recommending surgical intervention (18, 19, 22–25, 27). Most commonly, a woman who has not aborted and is awaiting delayed expulsion will no longer feel pregnant or have medication-induced symptoms; the patient will be waiting for the onset of bleeding or cramping similar to anticipating the start of menses (28). Providers must differentiate this scenario from women who have incomplete expulsion of the pregnancy tissue, for whom symptoms can include prolonged and irregular bleeding episodes. Early trials of methotrexate and misoprostol showed that serial β-hCG evaluations did not aid in the diagnosis of incomplete abortion. All women with an incomplete abortion presented clinically, and the incomplete abortion was not diagnosed by increasing or plateaued β-hCG levels (40, 49, 50).

Understanding the difference between incomplete abortion and the normal course of medical abortion is important. The sole purpose of ultrasound examination after misoprostol administration is to determine whether the gestational sac is present. After expulsion, the uterus will normally contain ultrasonographically hyperechoic tissue consisting of blood, blood clots, and decidua. Rarely does this finding during medical abortion indicate a need for intervention. In the absence of excessive bleeding, providers can follow such patients conservatively (51).

Overall, large studies demonstrate that less than 1% of women undergoing medical abortion will need emergent curettage because of excessive bleeding

(13, 22, 52–54). Moreover, the risk of clinically significant bleeding and transfusion may be lower in women with pregnancies up to 49 days of gestation compared with those beyond 49 days (11); this relative risk will vary depending on the regimen used. Still, just as for women undergoing surgical abortion, surgical curettage must be available on a 24-hour basis for cases of hemorrhage. Clinicians who wish to provide medical abortion services either should be trained in surgical abortion or should work in conjunction with a clinician who is trained in surgical abortion.

Clinical Considerations and Recommendations

▶ *What factors determine whether a woman is a candidate for medical abortion?*

Gestational Age

The upper limit of gestational age at which a medical abortion regimen is still an option varies depending on the types, dosages, and routes of administration of the medications. Outpatient treatment with mifepristone–misoprostol regimens up to 63 days of gestation and for methotrexate–misoprostol regimens up to 49 days of gestation are highly effective. Complete abortion rates among all regimens are highest for earlier gestations and are clinically similar in women with pregnancies up to 49 days of gestation. Between 50 and 63 days of gestation, the use of vaginal misoprostol in regimens with mifepristone results in complete abortion in 96–99% of women (18, 22–24, 26, 27, 43, 53, 55), whereas regimens using oral misoprostol demonstrate significantly lower success rates for these gestational ages.

Contraindications

Medical contraindications to abortion with mifepristone regimens include confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass, intrauterine device in place, current long-term systemic corticosteroid therapy, chronic adrenal failure, severe anemia, known coagulopathy or anticoagulant therapy, and mifepristone intolerance or allergy. Most clinical trials also exclude women with severe liver, renal, or respiratory disease, uncontrolled hypertension, cardiovascular disease (angina, valvular disease, arrhythmia, or cardiac failure), or severe anemia. Misoprostol should not be used in women with an uncontrolled seizure disorder or those who have an allergy or intolerance to misoprostol or other prostaglandins. Asthma is not a contraindication because misoprostol is a weak bronchodilator.

Although medical contraindications are infrequent, social or psychologic contraindications to medical abortion are more common. Women are not good candidates for medical abortion if they do not wish to take responsibility for their care, are anxious to have the abortion over quickly, cannot return for follow-up visits, or cannot understand the instructions because of language or comprehension barriers. Other nonmedical criteria to be considered are access to a phone in case of an emergency and access to 24-hour emergency medical treatment (eg, surgical curettage for hemorrhage). Counseling should include a description of cramping and bleeding and should indicate that, rarely, the process may not be completed for several weeks.

▶ *Which pretreatment laboratory tests are needed?*

No special pretreatment laboratory tests are necessary for medical abortion beyond those for surgical abortion. Confirmation of pregnancy by ultrasonography or pregnancy testing is necessary before attempting abortion regardless of method. Pretreatment assessment of hemoglobin or hematocrit and blood typing are imperative, and anti-D immune globulin should be administered if indicated.

▶ *What is the risk of infection with medical abortion?*

Endometritis is a rare complication of medical abortion. In trials involving more than 500 participants, infection rates typically vary from 0.09% to 0.6% (11, 17, 18, 22, 23, 27, 56, 57). No data exist to support the universal use of prophylactic antibiotics for medical abortion. Five cases of death have been reported in women using mifepristone, 200 mg, followed by misoprostol, 800 μg vaginally, in North America since 2001; all appear to be infectious, with *Clostridium sordellii* identified in three of the cases (58). The cause of these infections and the relationship of the deaths to mifepristone and misoprostol are still under investigation. Even if related, the death rate would be less than 1 per 100,000 mifepristone procedures, a rate comparable to that for early surgical abortion and miscarriage (59).

▶ *Is ultrasonography useful in the medical management of abortion before treatment?*

Gestational age should be confirmed by clinical evaluation or ultrasonography. Only 85% of U.S. women are able to predict gestational age within 2 weeks of the gestational age assigned by the clinician using ultrasound examination (60). Additionally, medical abortion studies in U.S. women have found that the gestational age determined by LMP was confirmed for only 40–60% of study participants (14, 27, 61). Because efficacy for some regimens decreases significantly with increasing gestational age, the clinical relevance of erroneous gestational age assignment will vary according to the regimen used.

Although not required, all major U.S. trials of mifepristone or methotrexate have relied on transvaginal ultrasonography for dating and follow-up. In France, however, clinicians use ultrasonography for preabortion screening only when they find a discrepancy between uterine size and dating by LMP and when patients present with bleeding or symptoms suggestive of ectopic pregnancy. Pregnancy termination services in France are offered only by authorized abortion clinics staffed by highly experienced providers. The high efficacy and safety results in the French trials suggest that this selective use of ultrasonography suffices when medical abortion is provided by experienced clinicians.

A concern when providing early abortion services is the possibility of an undiagnosed extrauterine gestation. Although the ectopic pregnancy rate in the general population is currently around 19–21 per 1,000 pregnancies (62, 63), ectopic pregnancy rates in studies of women seeking abortion are consistently lower. A study of surgical abortion in women with pregnancies less than 42 days of gestation in the United States found the ectopic pregnancy rate to be 5.9 per 1,000 pregnancies (64). Similarly, the largest published study of medical abortion involved 16,369 women with pregnancies up to 49 days of gestation, 21 of whom were excluded from the analysis because of an ectopic pregnancy, yielding an ectopic pregnancy rate of 1.3 per 1,000 pregnancies (57). Although ectopic pregnancy in a population of women seeking early abortion is rare, women with significant medical risk factors or history (eg, unilateral pain and vaginal bleeding) should have pretreatment ultrasonography.

▶ *What methods can be used to confirm complete abortion?*

Transvaginal ultrasonography offers an efficient means of assessing outcome in patients who undergo medical abortion. Its primary objective is to determine if the gestational sac is absent (with or without the presence of other ultrasonographically hyperechoic tissue). However, French clinicians, who have extensive experience with medical abortion, use ultrasonography significantly less than American clinicians (65). One explanation for this difference may be less familiarity with the process by both American clinicians and patients; another reason could be liability concerns in the United States. A study of U.S. providers indicated that ultrasonography is perceived to be unnecessary to assess abortion outcome for most women (66). Researchers asked physicians if they felt comfortable with their assessment without ultrasonography or if they would feel better in that situation with an ultrasound examination to confirm their impression based on the patient's history and physical examination. Physicians thought an ultrasound examination was not needed in 60% of the women who were ultimately found to have expelled the gestational sac. However, the gestational sac was still present in 29% of women for whom physicians believed ultrasonography was not indicated.

Methods to verify abortion include reports of bleeding combined with evidence of uterine involution on pelvic examination or hCG testing. When misoprostol is administered 2–5 days after methotrexate or mifepristone, β-hCG concentrations should decrease by at least 50% within 1 week of initiating the medication regimen. However, performing sensitive serum or urine hCG assays (detection threshold, 25–50 mIU/mL) too soon after the termination of a pregnancy may result in an erroneous diagnosis of failed medical abortion. Two trials using methotrexate and misoprostol found that the average time to disappearance of β-hCG is 33–34 days and may take as long as 90 days (40, 67). The utility of nonsensitive urine hCG assays in follow-up after mifepristone and misoprostol administration warrants investigation.

In clinical trials with methotrexate and misoprostol, only about half of the women who thought they had aborted actually had done so (28). Moreover, women may experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac (28), or even an ectopic pregnancy (22). The importance of patient follow-up must be emphasized because failure rates for medical abortion are higher than those for surgical techniques.

However, recent data suggest that for most women having an abortion with mifepristone and misoprostol, no follow-up may be needed other than a telephone conversation. One report compared clinicians' and patients' impressions of whether or not expulsion occurred based solely on the patient's history with the results of vaginal ultrasonography performed approximately 1 week after initiating treatment (68). When the clinician and the patient both thought that expulsion had occurred, they were correct 99% of the time. Additional studies are needed to validate the premise that such women need only a home pregnancy test for follow-up and that office evaluation should be required only if either the clinician or the patient is not certain that expulsion has occurred.

▶ *Do nonsteroidal antiinflammatory drugs affect the success rates for medical abortion?*

Cramping pain for patients who are not undergoing abortion usually is treated with ibuprofen or other non-steroidal antiinflammatory drugs (NSAIDs). Although NSAIDs inhibit the synthesis of new prostaglandins, they do not block the action of prostaglandin receptors; therefore, such agents should not inhibit the action of a prostaglandin used for medical abortion. The only report to evaluate the effects of analgesics on abortion outcome was a retrospective analysis of NSAIDs and complete abortion in 416 women who received misoprostol following methotrexate for medical abortion of pregnancies up to 56 days of gestation (69). The use of ibuprofen did not seem to interfere with the action of misoprostol to induce uterine contractions and pregnancy expulsion. Therefore, NSAIDs such as ibuprofen are not contraindicated for women undergoing a medical abortion.

▶ *How should a patient be counseled about potential teratogenicity if a medical method fails to lead to abortion?*

Because teratogenicity of medical abortifacients becomes an important issue if the pregnancy continues, patients must be informed of the need for a surgical abortion in the event of a continuing pregnancy. There is no evidence to date of a teratogenic effect of mifepristone. However, methotrexate is an antimetabolite that can cause fetal anomalies (70, 71). Evidence suggests that misoprostol also can result in congenital anomalies when used during the first trimester, possibly due to mild uterine contractions resulting in decreased blood flow during organogenesis (72). Anomalies associated with misoprostol use that have been described in the literature include defects in the frontal or temporal bones (73) and limb abnormalities with or without Möbius sequence (masklike facies with bilateral sixth and seventh nerve palsy and frequently coincident micrognathia) (74–77). No conclusions regarding teratogenicity can be drawn from these reports because of the extremely small sample sizes.

▶ *Does medical abortion affect future fertility?*

Future fertility following medical abortion has been evaluated only within a 1-year period after medical abortion in a group of 93 women who received methotrexate and misoprostol for abortion (78). Although none of the women were actively attempting to achieve pregnancy, 25% became pregnant, a rate higher than would be expected for a group of women using contraception. By comparison, another report indicated a pregnancy rate of 13% within 1 year after a first surgical abortion (79).

Summary of Recommendations and Conclusions

The following recommendations are based primarily on good and consistent scientific evidence (Level A):

- Medical abortion should be considered a medically acceptable alternative to surgical abortion in selected, carefully counseled, and informed women.
- The FDA-approved protocol of 600 mg of mifepristone orally followed approximately 48 hours later by 400 μg of misoprostol orally is safe and effective for medical abortion through 49 days of gestation (calculated from the first day of the LMP).
- Compared with the FDA-approved regimen, mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 μg of misoprostol vaginally are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP.
- A methotrexate–misoprostol regimen is appropriate for medical abortion only in pregnancies up to 49 days of gestation. Women using this regimen may wait up to 4 weeks for complete abortion to occur.
- Mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 μg of misoprostol vaginally are generally preferred to regimens using methotrexate and misoprostol or misoprostol only for medical abortion.
- A patient can administer misoprostol safely and effectively, orally or vaginally, in her home as part of a medical abortion regimen.

The following recommendations are based primarily on limited scientific evidence (Level B):

- Because teratogenicity of medical abortifacients becomes an important issue if the pregnancy continues, patients must be informed of the need for a surgical abortion in the event of a failed abortion.
- Gestational age should be confirmed by clinical evaluation or ultrasonography.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Surgical curettage must be available on a 24-hour basis for cases of hemorrhage, even though less than

1% of women having a medical abortion will need a curettage because of excessive bleeding.

- Pretreatment anti-D immune globulin should be administered if indicated.
- No data exist to support the universal use of prophylactic antibiotics for medical abortion.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and June 2005. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.
II-1 Evidence obtained from well-designed controlled trials without randomization.
II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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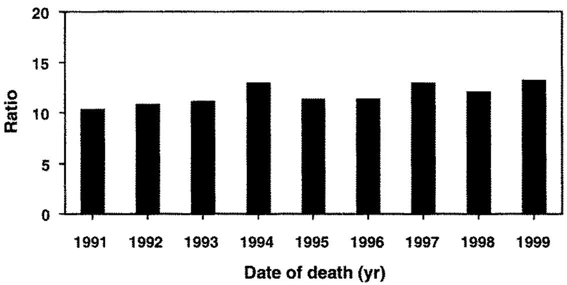
Pregnancy-Related Mortality Surveillance — United States, 1991–1999

Pregnancy-Related Mortality Ratios,* by Year of Death — United States, 1991–1999



*Deaths per 100,000 live births.

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CONTENTS

Introduction 2
Methods 2
Results 3
Discussion 6
Limitations 7
Public Health Measures 7
Acknowledgments 7
References 8

Pregnancy-Related Mortality Surveillance — United States, 1991–1999

Jeani Chang, M.P.H.
Laurie D. Elam-Evans, Ph.D.
Cynthia J. Berg, M.D.
Joy Herndon, M.S.
Lisa Flowers
Kristi A. Seed
Carla J. Syverson, M.N., M.P.H.
Division of Reproductive Health
National Center for Chronic Disease Prevention and Health Promotion

Abstract

Problem/Condition: The risk of death from complications of pregnancy has decreased approximately 99% during the twentieth century, from approximately 850 maternal deaths per 100,000 live births in 1900 to 7.5 in 1982. However, since 1982, no further decrease has occurred in maternal mortality in the United States. In addition, racial disparity in pregnancy-related mortality ratios persists; since 1940, mortality ratios among blacks have been at least three to four times higher than those for whites. The Healthy People 2000 objective for maternal mortality of no more than 3.3 maternal deaths per 100,000 live births was not achieved during the twentieth century; substantial improvements are needed to meet the same objective for Healthy People 2010.

Reporting Period Covered: This report summarizes surveillance data for pregnancy-related deaths in the United States for 1991–1999.

Description of System: The Pregnancy Mortality Surveillance System was initiated in 1987 by CDC in collaboration with state health departments and the American College of Obstetricians and Gynecologists Maternal Mortality Study Group. Health departments in the 50 states, the District of Columbia, and New York City provide CDC with copies of death certificates and available linked outcome records (i.e., birth certificates or fetal death certificates) of all deaths occurring during or within 1 year of pregnancy. State maternal mortality review committees, the media, and individual providers report a limited number of deaths not otherwise identified. Death certificates and relevant birth or fetal death certificates are reviewed by clinically experienced epidemiologists at CDC to determine whether they are pregnancy-related.

Results: During 1991–1999, a total of 4,200 deaths were determined to be pregnancy-related. The overall pregnancy-related mortality ratio was 11.8 deaths per 100,000 live births and ranged from 10.3 in 1991 to 13.2 in 1999. The pregnancy-related mortality ratio for black women was consistently higher than that for white women for every characteristic examined. Older women, particularly women aged $\geq$35 years and women who received no prenatal care, were at increased risk for pregnancy-related death. The distribution of the causes of death differed by pregnancy outcome. Among women who died after a live birth (i.e., 60% of the deaths), the leading causes of death were embolism and pregnancy-induced hypertension.

Interpretation: The reported pregnancy-related mortality ratio has substantially increased during 1991–1999, probably because of improved ascertainment of pregnancy-related deaths. Black women continued to have a 3–4 times higher pregnancy-related mortality ratio than white women. In addition, pregnancy-related mortality has the largest racial disparity among the maternal and child health indicators. Reasons for this difference could not be determined from the available data.

Public Health Actions: Continued surveillance and additional studies should be conducted to monitor the magnitude of pregnancy-related mortality, to identify factors that contribute to the continuing racial disparity in pregnancy-related mortality, and to develop effective strategies to prevent pregnancy-related mortality for all women. In addition, CDC is working with state health departments, researchers, health-care providers, and other stakeholders to improve the ascertainment and classification of pregnancy-related deaths.

Introduction

The reduction of maternal mortality is one of the Healthy People 2010 objectives for the United States. This objective is a public health priority with the same goal as the Healthy People 2000 objective of no more than 3.3 maternal deaths per 100,000 live births (*1–2*). The risk of death from complications of pregnancy decreased substantially during the twentieth century, from 850 maternal deaths per 100,000 live births in 1900 to 7.5 in 1982, according to official U.S. vital statistics (*3*). However, this progress halted in 1982, and the mortality ratio has fluctuated between seven and eight maternal deaths per 100,000 live births since that time (*4–5*). In addition, a continuing disparity exists in the risk for pregnancy-related death between black women and white women. The pregnancy-related mortality ratios (pregnancy-related deaths per 100,000 live births) for black women are 3–4 times higher than for white women (*6–10*). Prevention of mortality attributable to pregnancy is a primary public health objective. Pregnancy complications remain an important concern for clinical medicine and for the health-care system.

In 1987, CDC's Division of Reproductive Health, in collaboration with state health departments and the American College of Obstetricians and Gynecologists (ACOG) Maternal Mortality Study Group, established the Pregnancy Mortality Surveillance System (PMSS) (*11*). This system provides ongoing surveillance of all pregnancy-related deaths reported through individual state health departments, maternal mortality review committees, media, and individual providers. Therefore, PMSS permits increased precision in measuring the magnitude of pregnancy-related mortality and identifying the groups at increased risk of death than do systems relying on death certificate data alone. This report summarizes the analysis of identified pregnancy-related deaths in the United States during 1991–1999.

Methods

PMSS collects data regarding all reported deaths that are causally related to pregnancy. The first step is to identify all deaths occurring during pregnancy or within 1 year of pregnancy. Methods used to establish this temporal relation between pregnancy and a death included 1) a pregnancy check box had been marked on the death certificate, 2) the death certificate had indicated that the woman was pregnant at the time of death, or 3) the death certificate of the reproductive-aged woman had been matched with a birth certificate or fetal death certificate for a delivery that occurred within 1 year before the woman's death.

Health departments in the 50 states, the District of Columbia, and New York City voluntarily provided CDC with copies of death certificates that were causally related to pregnancy. For deaths that occurred after a live birth or stillbirth, the matching birth or fetal death certificates were also provided by the health departments. In addition to requesting certificates of deaths that are causally related to pregnancy, beginning with deaths occurring in 1991, states were asked to send certificates of all deaths that occurred during pregnancy or within 1 year of pregnancy, regardless of the cause of death or relation between pregnancy and the death. Pregnancy-related deaths occurring during 1991–1999 are reported because these are the most recent data available that have not been published previously in an *MMWR Surveillance Summary*.

Data were coded after review of all available information from death certificates (including notes written on the margins of death certificates), maternal mortality review committee reports, autopsy reports, and matched birth and fetal death certificates. Matched birth certificates or fetal death certificates were available for the majority of women who delivered a live-born or stillborn infant. These certificates provided information not otherwise available on the death certificate (e.g., prenatal care and live birth order). Data concerning all deaths were reviewed and classified by clinically experienced medical epidemiologists at CDC regarding the immediate and underlying cause of death, associated obstetric conditions, and the outcome of pregnancy.

In this report, a woman's death was classified as pregnancy-related if it occurred during pregnancy or within 1 year of pregnancy and resulted from 1) complications of the pregnancy, 2) a chain of events that was initiated by the pregnancy, or 3) the aggravation of an unrelated condition by the physiologic effects of the pregnancy or its management (*11*).

Pregnancy-related mortality ratios were calculated by using the number of deaths obtained from the PMSS (numerator) and live-birth data (denominator) obtained from the 1991–1999 national natality files compiled by CDC's National Center for Health Statistics (*12*). This standard live-birth population included all women who delivered a live birth during 1991–1999.

For both the numerator and the denominator of pregnancy-related mortality ratios, race was defined as the race of the mother and classified as white, black, or other. Other races included Asian/Pacific Islander, American Indian/Alaska Native, and those reported as other. All pregnancy-related deaths of women with unknown races (n = 19) were proportionally redistributed into known categories. Because of the limited number of pregnancy-related deaths in the other race category (n = 208), data regarding other race were not included for race-specific analyses.

The women's ages at the time of death were grouped into standard 5-year intervals. Education information was obtained from either the death, birth, or fetal death certificates and was based on the total years of education completed at the time of death. The analysis of education was restricted to women aged ≥ 20 years, an age by which the majority of women would have had the opportunity to graduate from high school. The state of Georgia did not report maternal education during 3 years of the surveillance period (1997–1999); therefore, women who died in Georgia were excluded from analyses by education. Marital status was categorized as married (currently married) or unmarried (never married, divorced, separated, or widowed).

Information concerning prenatal care and live-birth order were limited to women who delivered a live-born infant, because these data were not consistently available for women who had a stillbirth or abortion. Onset of prenatal care was categorized as initiation in the first, second, and third trimesters, or no prenatal care. Live birth order, defined as the number of live births including the index pregnancy in which the woman had delivered, was used as a proxy for parity. Time interval, defined as number of days between the end of pregnancy and maternal death, was calculated and used as a categorical variable.

All analyses were performed by using SAS® software system *(13)*. Logistic regression was based on maximum likelihood estimation methods and used to test the significance of the change in mortality ratios over time and to compute 95% confidence intervals and associated p values. However, because of the high number of live births in each year (approximately 4 million live births per year), a limited increase in the mortality ratio over time could lead to a statistically significant result. Ninety-five percent confidence intervals were provided for risk ratios by using the associated standard errors *(14)*. Unless otherwise stated, all p values <0.05 were considered statistically significant.

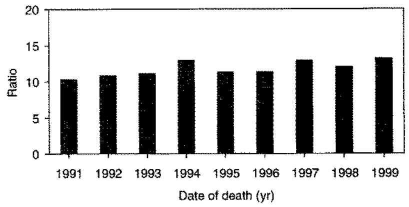
Results

During 1991–1999, a total of 7,342 deaths were reported to PMSS. Of these, 2,919 deaths occurred during pregnancy or within 1 year of pregnancy but were not causally related to pregnancy. Although causally related to pregnancy, 106 deaths were excluded from this analysis because the time interval between the end of pregnancy and maternal death exceeded 1 year, and 117 deaths were excluded because whether the death was related to a pregnancy was unknown. The remaining 4,200 deaths were used as the basis for this analysis. A matched birth certificate was available for 93% of deaths that occurred after a live birth, and a matched fetal death certificate was available for 88% of deaths that occurred after a stillbirth.

The overall pregnancy-related mortality ratio was 11.8 deaths per 100,000 live births for the 9-year surveillance period. The ratio significantly increased from 10.3 in 1991 to 13.2 in 1999 ($p<0.001$ for trend) (Figure 1). The pregnancy-related mortality ratio differed by maternal age; the risk for pregnancy-related death increased substantially among women aged ≥ 35 years (Table 1). Women aged ≥ 40 years had a pregnancy-related mortality ratio that was two times higher than that among women aged 35–39 years and approximately 4 times higher than women aged 30–34 years. Race was strongly associated with pregnancy-related mortality; black women were approximately four times more likely to die from pregnancy-related causes than were white women (Table 1).

Race-specific pregnancy-related mortality ratios were higher for black women than for white women of all ages (Figure 2). In comparison with pregnancy-related mortality ratios for white women, excess risk for black women increased substantially with age and was most evident at aged >39 years (i.e., the ratio was 5.5 times higher for black women). Overall, the risk for pregnancy-related death among unmarried women was higher than that among married women (Figure 3). However, the pattern of this risk differed for black women and white women. The mortality ratio for black married women

FIGURE 1. Pregnancy-related mortality ratios,* by year of death — United States, 1991–1999



*Deaths per 100,000 live births.

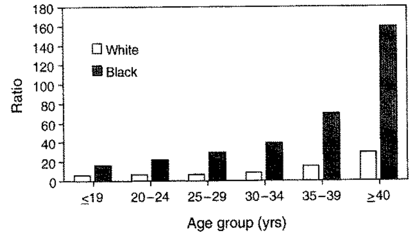
TABLE 1. Pregnancy-related mortality ratios (PRMR)* and risk ratios, by age group and race — United States, 1991–1999

Category	No. deaths	PRMR	Risk ratio	95% C.I.†
Age group (yrs)				
≤19	393	8.6	Referent	
20–24	863	9.6	1.1	(0.8–1.5)
25–29	938	9.4	1.1	(0.8–1.5)
30–34	968	12.0	1.4	(1.1–1.8)
35–39	749	21.6	2.5	(2.0–3.2)
≥40	289	45.4	5.3	(4.2–6.6)
Race				
White	2,293	8.1	Referent	
Black	1,699	30.0	3.7	(2.9–4.7)

*Deaths per 100,000 live births.

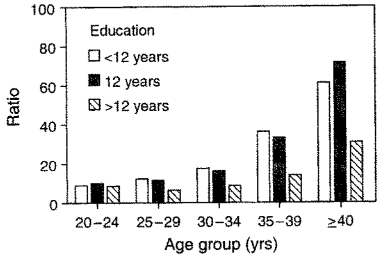
†Confidence interval.

FIGURE 2. Pregnancy-related mortality ratios,* by age and race — United States, 1991–1999



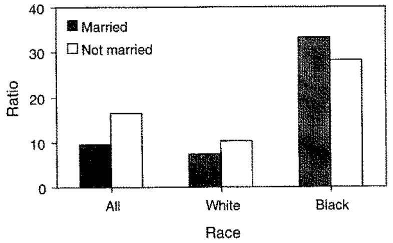
* Deaths per 100,000 live births.

FIGURE 4. Pregnancy-related mortality ratios,* by age and education† — United States, 1991–1999



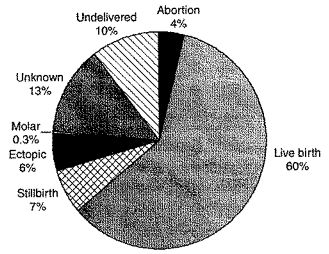
* Deaths per 100,000 live births.
† Excludes women aged <20 years and excludes women who died in Georgia.

FIGURE 3. Pregnancy-related mortality ratios,* by race and marital status — United States 1991–1999



* Deaths per 100,000 live births.

FIGURE 5. Distribution of pregnancy-related deaths, by outcome of pregnancy — United States, 1991–1999



was higher than that for black unmarried women; the ratio was lower for white married women compared with white unmarried women. Overall, women who had >12 years of education had the lowest pregnancy-related mortality ratio. The risk for pregnancy-related death decreased with increasing levels of education among women aged 25–39 years (Figure 4). At all levels of education, pregnancy-related mortality ratios for black women were 3–4 times higher than ratios for white women.

The most frequent pregnancy outcome associated with a pregnancy-related death was live birth (60%), followed by undelivered pregnancy (10%), and stillbirth (7%) (Figure 5). The outcome of pregnancy at the time of death was not known for 552 (13%) of the women. The only significant differences between black and white women in relation to pregnancy outcomes was the higher percentage of ectopic pregnancy (8%) among black women than among white women (4%) ($p<0.001$). Of women who died after a live birth, 4% had not received any prenatal care, and 24% had missing data regarding prenatal care. Mortality ratios for each trimester of prenatal-care initiation were 3–4 times higher for black women than for white women (Table 2). Overall, the pregnancy-related mortality ratio was 3–4 times higher among women who received no prenatal care compared with women who received any prenatal care. Women who received no prenatal care were more likely to have had ≥5 previous live births and have fewer years of education.

Among women whose pregnancies resulted in a live birth, the risk for pregnancy-related death increased with increasing live-birth order (Table 2). For both white and black women, the pregnancy-related mortality ratios were approximately 2 times higher for women after the delivery of a fifth or higher live birth than for women after a first live birth. Overall, a three- to fourfold disparity exists in pregnancy-related deaths for black women compared with white women for each level of parity.

The leading causes of pregnancy-related death were embolism (20%), hemorrhage (17%), and pregnancy-induced hy-

TABLE 2. Race-specific pregnancy-related mortality ratios*, by trimester of prenatal care initiation and live-birth order — United States, 1991–1999

Category	Pregnancy-Related mortality ratio White	 Black	 All deaths
Prenatal care initiation (trimester)			
First	3.6	13.1	5.0
Second	4.4	12.7	6.5
Third	3.7	10.9	5.8
No care	14.9	29.1	19.8
Unknown	55.2	111.0	69.5
Live-birth order			
First	3.1	10.7	4.2
Second	3.3	14.1	5.0
Third	4.8	14.2	6.5
Fourth	6.3	15.7	8.7
Fifth or more	7.6	22.2	11.6

*Pregnancy-related deaths among women who delivered a live-born infant per 100,000 live births.

pertension (16%) (Table 3). Although the percentages of all pregnancy-related deaths attributable to these causes have gradually decreased in the previous two decades, the percentage of deaths attributable to cardiomyopathy increased from 6% in 1991 to 9% in 1999. However, this increase was not statistically significant. Deaths attributable to other medical conditions have significantly increased from 14% in 1991 to 20% in 1999 ($p<0.05$). Deaths attributable to other medical conditions consist primarily of cardiovascular problems (34%), pulmonary problems (11%), and neurologic or neurovascular problems (7%). The leading causes of death differed by pregnancy outcome (Table 3). The leading causes of death among women who died after a live birth were embolism (21%), pregnancy-induced hypertension (19%), and other medical conditions (17%). Among women whose pregnancies ended in a stillbirth, the leading causes of death were hemorrhage (21%) (from abruptio placenta and uterine rupture), pregnancy-induced hypertension (20%), and infection (19%). Hemorrhage accounted for 221 (93%) of 237 deaths associated with ectopic pregnancies. Among women whose pregnancies ended in a spontaneous or induced abortion, infection was the cause of death for 34% of the women, followed by hemorrhage (22%) and other medical conditions (16%). Women who were still pregnant (undelivered) at the time of death most frequently died from other medical conditions (e.g. cardiovascular and neurologic problems) (34%) and embolism (25%), mostly thrombotic.

Embolism, hemorrhage, and pregnancy-induced hypertension were the leading causes of death for both white and black women. The cause-specific, pregnancy-related mortality ratio was approximately 3–4 times higher for black women compared with white women for each cause of death. However, the risk for death as a result of cardiomyopathy and complications of anesthesia was 6 times higher for black women than for white women.

Information regarding the time interval between the end of pregnancy and death was known for 3,378 (80%) of 4,200 maternal deaths. Of these, 1,160 (34%) women died within 24 hours after the end of their pregnancy; 1,845 (55%) deaths occurred during 1–42 days of pregnancy; and 11% died during 43–365 days. In addition, time interval varied by cause of death (Figure 6). Among women who died from embolism, the majority of deaths (52%) occurred within 24 hours after the pregnancy ended, and 68% of deaths attributed to hemorrhage occurred within 48 hours after the pregnancy ended.

TABLE 3. Causes of pregnancy-related death, by outcome of pregnancy and pregnancy-related mortality ratios (PRMR*) — United States, 1991–1999

Cause of death	Outcome of pregnancy (% distribution) Live birth (n = 2,519)	 Stillbirth (n = 275)	 Ectopic (n = 237)	 Abortion† (n = 165)	 Molar (n = 14)	 Undelivered (n = 438)	 Unknown (n = 552)	All outcomes % (N = 4,200)	 PRMR
Embolism	21.0	18.6	2.1	13.9	28.6	25.1	18.3	**19.6**	**2.3**
Hemorrhage	2.7	21.1	93.3	21.8	7.1	8.7	8.7	**17.2**	**2.0**
PIH§	19.3	20.0	0	0.6	0	12.3	11.8	**15.7**	**1.8**
Infection	11.7	18.9	2.5	33.9	14.3	11.0	12.9	**12.6**	**1.5**
Cardiomyopathy	10.1	5.1	0.4	1.8	0	3.4	11.2	**8.3**	**1.0**
CVA¶	5.7	0.7	0	1.2	0	3.9	8.5	**5.0**	**0.6**
Anesthesia	1.8	0.7	1.3	9.7	0	0	0.4	**1.6**	**0.2**
Other**	17.1	14.9	0.4	16.4	50.0	33.6	27.9	**19.2**	**2.3**
Unknown	0.6	0	0	0.6	0	2.1	0.4	**0.7**	**0.1**
Total††	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**11.8**

* Pregnancy-related deaths per 100,000 live births.

† Includes spontaneous and induced abortions.

§ Pregnancy-induced hypertension.

¶ Cerebrovascular accident.

** The majority of the other medical conditions were cardiovascular, pulmonary, and neurologic problems.

†† Percentages might not add to 100.0 because of rounding.

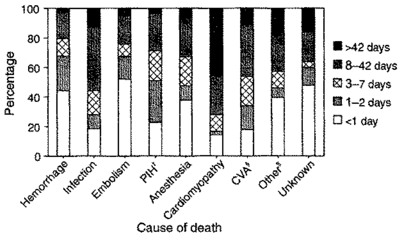
Of the 116 women who died as a result of cardiomyopathy, 45% died during 43–365 days after the end of pregnancy.

Discussion

The Healthy People 2000 and Healthy People 2010 objectives address the same goal for reducing maternal deaths to 3.3 maternal deaths per 100,000 live births (*1–2*). However, this goal was not met by the year 2000, and substantial improvement is needed to attain the goal by 2010. The pregnancy-related mortality ratios reported by the PMSS increased from 10.3 deaths per 100,000 live births in 1991 to 13.2 in 1999. This increase in the pregnancy-related mortality ratio probably reflects the enhanced ascertainment of cases for this surveillance system (e.g., increased use of linkages, pregnancy check boxes, and the new request to identify all deaths during pregnancy or within 1 year of pregnancy).

Embolism, hemorrhage, and pregnancy-induced hypertension complications were the leading causes of pregnancy-related deaths during 1991–1999 (*7*). Although a substantial reduction in the percentage of deaths attributable to these causes has occurred during the previous two decades (*9,15*), the percentage of deaths attributable to cardiomyopathy and other medical conditions increased during the surveillance period (*16*). The increase in the number of cardiomyopathy-related deaths and deaths attributable to other medical conditions likely reflects improved ascertainment of pregnancy-related deaths by linking death certificates of women to live and stillbirths occurring within 1 year of the mother's death. The increasing number of deaths caused by other medical conditions might also be affected by changes in the age distribution of women giving birth. Women in the United States are becoming pregnant at older ages, and the prevalence of chronic medical conditions increases with age (*17–18*). In addition, older women are at increased risk for pregnancy-related death (*7–10*) and adverse reproductive health outcomes, particularly women aged ≥35 years (*17,19*).

FIGURE 6. Distribution of pregnancy-related deaths, by cause of death and time interval* — United States, 1991–1999



* Number of days between the end of pregnancy and maternal death.
† Pregnancy-induced hypertension.
§ Cerebrovascular accident.
¶ The majority of the other medical conditions were cardiovascular, pulmonary, and neurologic problems.

Pregnancy-related mortality ratios continued to be 3–4 times higher for black women than for white women (*6–10*). In addition, the pregnancy-related mortality ratios for black women aged >39 years were particularly high in comparison with white women in the same age group (*7,19*). The risk for pregnancy-related death resulting from cardiomyopathy and complications of anesthesia were both approximately 6 times higher for black women than for white women.

Among women aged ≥20 years, higher levels of education were associated with decreasing pregnancy-related mortality ratios; however, pregnancy-related deaths for black women were 3–4 times higher than that for white women at any education level. Although the overall risk for pregnancy-related death was higher among unmarried women than among married women, this association varied by race. Black married women had a higher mortality ratio than black unmarried women, and the inverse was observed for white women.

Of all maternal deaths that occurred after a live birth, 56% of the women received early prenatal care (i.e., during the first trimester) as recommended (*20*), but 4% received no prenatal care at all. Overall, women who received any prenatal care have a lower risk for pregnancy-related mortality in comparison with women who received no prenatal care. Pregnancy-related mortality ratios for black women were higher at each level of prenatal-care initiation than ratios for white women. In addition, the reduction in mortality ratios among women who received prenatal care compared with women who received no prenatal care was higher among white women than among black women. Differences exist, by race, in the content of prenatal care for black women and white women (*21–24*); black women often receive fewer services and insufficient health-promotion education during their prenatal visits (*24–27*). However, the relation between these prenatal care indicators (i.e., content of prenatal care and number of visits) and pregnancy-related mortality is not clear.

The characteristics evaluated in this report confirmed the racial disparity in pregnancy-related deaths, but the reasons for disparities could not be determined from the available data. Whether the racial disparity might be related to differences in the seriousness of morbidity, differences in diagnosis and treatment of pregnancy-related complications, or a combination of these factors is unclear. These factors, although not measurable through routine surveillance, probably contributed to the increased risk for pregnancy-related death among black women. Race might also serve as a marker for other sociodemographic risk factors and cultural differences (*28–30*). However, the sources from which data were obtained for this surveillance system had limited information concerning sociodemographic indices, family and community conditions, and other factors that might be associated with the differences in pregnancy-related mortality between black and white women.

Limitations

Limitations should be considered in the analysis of pregnancy-related mortality during 1991–1999. Although ascertainment methods have improved, pregnancy-related deaths were undetected (*9,16,31–35*). Because this report is based on data provided voluntarily by state health departments in the 50 states, the District of Columbia, and New York City (which registers births and deaths separately from New York state), methods used to identify death certificates differed by reporting area.

For 1991–1998, the majority of reporting areas identified deaths by the *International Classification of Diseases, Ninth Revision* (ICD-9), codes 630–676 (*36*). Beginning in 1999, the *International Classification of Diseases, Tenth Revision* (ICD-10), was used; however, the use of ICD-10 has not been fully implemented by all reporting areas. Seventeen reporting areas include a check box on their death certificate to indicate whether pregnancy had recently occurred (*37*). The inclusive time interval (i.e., interval between the end of pregnancy and death) used in the check box is inconsistent and varies by state, from 42 days to 18 months. Using a check box has been helpful for health departments to identify additional deaths that occurred during a specified time frame (*37*). However, death certificates ascertained by check box alone did not contain enough information to establish that a causal relation also existed between pregnancy and death. In addition, the increased use of linkages of death certificates of women of reproductive age to live birth or fetal death records occurring within the year before death substantially improves ascertainment of pregnancy-related deaths associated with live-birth or fetal-death outcomes (*16,31–33,38*). However, this linkage of vital records does not identify pregnancy-related deaths that do not generate a record of pregnancy outcome (e.g., ectopic pregnancies and undelivered events) (*39*).

Although having the matched birth or fetal death certificates with maternal death certificates improved the quality and quantity of the available information regarding the pregnancy-related deaths, the assessment of circumstances leading to pregnancy-related death was limited by the absence of detailed clinical data. Pregnancy-related death encompasses a complex combination of etiologies and pregnancy outcomes, and the underlying risk factors associated with death vary with cause of death and pregnancy outcome. A more accurate classification can be made if the medical information (the lower section of the birth record) is included, but this information is not consistently provided. In addition, certain states are now providing to CDC computer-generated reports that do not include details needed to optimally classify deaths. However, CDC is working with state health departments, researchers, health-care providers, and other stakeholders to improve the ascertainment and classification of pregnancy-related deaths.

Public Health Measures

Although deaths attributable to pregnancy are rare, each death needs to be identified and carefully reviewed at the state level. To accurately identify causes of pregnancy-related mortality in the United States, complete and consistent reporting is needed (*40*). Additional sources of data, including review of the medical and social circumstances of the death, are necessary to understand the effects of medical care, socioeconomic status, access to and content of prenatal care, social environment, and lifestyle on the sequence of events that lead to pregnancy-related deaths.

The continuing disparity in pregnancy-related mortality between white and black women indicates the need to identify the differences that contribute to excess mortality among black women. Specific interventions should be developed to reduce pregnancy-related mortality, especially among black women.

Pregnancy-related deaths are underreported, and the true number of deaths related to pregnancy might increase from 30%–150% with active surveillance (*16,31–33*). Therefore, improved surveillance and additional research are needed to assess the magnitude of pregnancy-related deaths, further identify potential risk groups, and investigate the causal pathway that led to the death (*41*). The use of ICD-10 and the revised death certificate will assist in identifying additional maternal deaths. The proposed revision includes a pregnancy check box as a standard element with designated time intervals between the end of pregnancy and death to more effectively identify deaths that are potentially associated with pregnancy.

This report provides results from a national population-based data set with sufficient numbers to examine trends and major risk factors for pregnancy-related mortality. It provides information that is needed to develop effective strategies to prevent pregnancy-related mortality for all women.

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SPECIAL REPORT

Abortion Reporting in the United States: An Examination of the Federal-State Partnership

By Rebekah Saul

Over the past three years, several events have led policymakers, public health officials and the general public to focus renewed attention on abortion data in the United States. The information that is available on how many abortions are performed, when they take place and what methods are used has contributed to the public policy debate, but it also has proven inadequate in some instances to answer all the questions being asked.

For example, in 1995 Ohio outlawed dilation and extraction abortions, an event seen by opponents of abortion as the first victory in a national campaign to ban procedures they later dubbed "partial birth" abortions. The proposed federal "Partial-Birth Abortion Ban Act" has intensified the debate over abortion procedures, late-term abortions and, ultimately, the incidence and timing of abortions in general. Yet the debaters were often frustrated because specific data on the frequency of late-term abortions are limited, and data on the use of dilation and extraction do not exist either at the state or national level.

Moreover, at around the same time, Congress enacted a federal welfare reform law, the Personal Responsibility and Work Opportunity Reconciliation Act of 1996. Among several provisions intended to discourage out-of-wedlock births is the so-called illegitimacy bonus: Every year, for the next four years, the federal government will award $20 million each to the five states that can demonstrate the largest reduction in out-of-wedlock births and a simultaneous decrease in abortion rates. While the legislation establishes 1995 as the baseline against which reductions and increases will be measured, it does not address the limitations of abortion data collection efforts, which pose a significant challenge for accurately establishing a baseline level of abortion in many states, as well as for establishing accurate subsequent levels.

In 1996, as well, the Food and Drug Administration (FDA) took significant steps toward approving the use of medical (nonsurgical) abortion in the United States, essentially by "preapproving" the use of mifepristone, popularly known as RU 486, as an abortifacient; final approval is pending information on manufacturing and labeling. In addition, FDA cleared the way for clinical study by U.S. health care providers of a combination of two other drugs—methotrexate and misoprostol—used to induce early nonsurgical abortions.

While it remains to be seen to what extent the advent of medical (nonsurgical) abortions will actually change the provision of abortion services in the United States, it is at least possible that such abortions will be administered by health care providers who, for whatever reasons, have been reluctant to provide surgical abortions. If new providers do indeed emerge, incorporating abortion reporting by these providers into current reporting procedures will be critical both to measuring the number of abortions provided in the United States, and to monitoring the drugs' use and safety. Furthermore, because medical abortion is used primarily in the first seven weeks of pregnancy, the provision of nonsurgical abortion may lead to a shift in the timing of abortions. Documenting this shift might prove important to the abortion debate, since many individuals support early abortion but grow increasingly uncomfortable with the procedure as the pregnancy continues.

The Centers for Disease Control and Prevention (CDC), the government agency currently responsible for compiling U.S. abortion data, has been criticized by some people for its inability to answer all abortion-related inquiries—particularly, detailed questions relating to late-term abortions. However, such criticism does not consider that—in keeping with vital statistics tradition—CDC obtains its data through a voluntary federal-state partnership in which states are responsible for collecting and managing data in accordance with their own policies and systems, and submitting the information to the federal government. As a result, states ultimately determine the quality and availability of national, government-generated abortion data.

Background

History of U.S. Vital Statistics

The maintenance of vital records in the United States dates back to the 1600s, when colonies voluntarily or by law kept registers of births, deaths and marriages. This early recordkeeping was done primarily to protect individual rights; records were regarded as legal documents necessary for posterity and to ensure just administration of inheritance and other laws. During the 17th and 18th centuries, recognition of the utility of vital records as a public health tool grew, and local health boards began using death records to trace epidemics and evaluate community health.[1]

In the 1800s, several states and cities adopted laws governing the organization of public health agencies, and government maintenance of vital statistics emerged as an important public health function. Congress created the National Board of Health, which (in conjunction with the U.S. Bureau of the Census) was to spearhead establishment of a national vital statistics system. By 1900, the Census Bureau had developed the first standard certificates of birth and death, and in 1907 submitted the first in a series of model vital statistics bills to the states.

In 1946, responsibility for national vital statistics was transferred from the Census Bureau to the U.S. Public Health Service, which made two significant moves a decade later: It developed and issued the first standard records of marriage and di-

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Rebekah Saul is public policy associate with The Alan Guttmacher Institute, Washington, D.C.

vorce or annulment, and it issued the Certificate of Fetal Death (which later became the U.S. Standard Report of Fetal Death).

The National Center for Health Statistics (NCHS) was established in 1960 to collect statistics on a broad range of health topics, to conduct relevant research and analysis, and to publish vital statistics data. Nevertheless, the primary responsibility for collecting, managing and compiling vital records—records of births, deaths, fetal deaths, marriage and divorce or annulment—lies with the states in accordance with their own laws, regulations and public health agencies. They also submit data to the federal government on a contractual basis, through which the federal government shares in the cost of operating the state system.

Reporting Abortions

The move toward legalization of induced abortion in several states during the late 1960s provided an impetus for distinguishing between spontaneous and induced termination of pregnancy in reporting. As a result, some states began to collect induced abortion data separately, while others continued to record the events as fetal deaths. In 1969, with the original intent of monitoring the safety of abortion, CDC initiated a national abortion surveillance system to compile and analyze state-generated abortion statistics.[2]

Around the time of the landmark 1973 U.S. Supreme Court decision in *Roe v. Wade*, which legalized abortion in the United States, NCHS stepped up its efforts to obtain abortion data by attempting to install an abortion reporting system on par with other vital statistics data collection. In 1978, as part of that effort, NCHS introduced a standard form specifically for the reporting of induced abortion—the U.S. Standard Report of Induced Termination of Pregnancy. It was hoped that the NCHS system of collecting abortion data, which utilized micro data sets obtained by NCHS from the states on a contractual basis, would eventually replace the CDC abortion surveillance system, which relies on state-reported aggregate data.

However, NCHS was under severe financial constraint and failed to fund its abortion program adequately. This problem stymied the abortion data system's growth. At its peak, NCHS obtained abortion data from only 15 states, and the program was discontinued altogether after data year 1993.

Today, CDC's abortion surveillance system remains the sole governmental source of abortion data. The primary responsibility for recording, collecting and managing data rests with the states' vital statistics agencies, which submit data to CDC on a voluntary basis. CDC retains the federal role of issuing model legislation, forms and guidelines, as well as compiling and publishing state information; however, CDC does not share in the cost of the state data collection. Most recently, with the advent of medical abortion using such drugs as mifepristone and methotrexate, CDC led the effort to revise the U.S. Standard Report of Induced Terminations of Pregnancy to include medical abortions as a type of procedure.

Challenges to Abortion Reporting

Over time, all 50 states have wrestled with abortion reporting requirements, because, as with all abortion-related issues, reporting has met with controversy. At the heart of the issue is whether induced abortions should be regarded as reportable events paralleling births, deaths and fetal deaths, or rather as health events to be monitored as other surgeries and medical procedures are.

Additionally, some abortion rights supporters have raised concerns about the intent of abortion reporting requirements. They fear that abortion foes will use the laws to deter abortion provision, either by making reporting requirements too onerous or by allowing reported data to be used to harass service providers or women who have obtained abortions. In several states, reporting policies have been legally challenged; two cases argued before the Supreme Court have upheld reporting requirements.

When the Supreme Court heard challenges to Missouri's 1974 abortion law in *Planned Parenthood of Central Missouri v. Danforth*, the justices unanimously upheld the law's requirements that all health facilities and physicians report all abortions to the health departments. The Court concluded that such recordkeeping is useful to the state's interest in protecting the health of its female citizens, and that recordkeeping and reporting requirements "that are reasonably directed to the preservation of maternal health and that properly respect a patient's confidentiality and privacy are permissible."[3]

Sixteen years later, the Supreme Court reiterated its position in *Danforth* when it decided on the reporting requirement provisions of the Pennsylvania Abortion Control Act in *Planned Parenthood of Southeastern Pennsylvania v. Casey*. The decision stated that "[t]he collection of information with respect to actual patients is a vital element of medical research, and so it cannot be said that the requirements serve no purpose other than to make abortions more difficult."[4] These decisions largely affirmed states' moves to institutionalize the reporting of abortion data.

Data Completeness and Quality

While issues related to the quality of abortion data are outside the scope of this article, two studies that examined the completeness and consistency of state abortion data deserve mention. They highlight some of the limitations of abortion data, as well as indicate the potential impact of provider education and outreach, enforcement, follow-up and quality monitoring on state abortion data.

The first points to the underreporting and nonreporting that may occur in some states. The 1980 study compared Tennessee abortion data reported by providers to the Tennessee Department of Public Health with data reported for the state by The Alan Guttmacher Institute (AGI), which collects abortion data by surveying providers directly.[5] For 1974, the Tennessee Department of Public Health reported only half the number of abortions that AGI reported.

The authors concluded that "underreporting, or more specifically, nonreporting, by some facilities in Tennessee, has occurred because clinic and hospital administrators did not know that they were responsible for reporting abortions performed at their facilities and they have relied on physicians to do so." In subsequent years, according to the authors, department of health staff informed nonreporting clinics of the law, and by 1976 the department reported 74% of the number of abortions that AGI reported.

The second study illustrates the problems that arise both from measuring rare events and from human error: A few misrecorded abortions in Georgia dramatically altered the state's data on third-trimester abortions. The authors analyzed the accuracy of data on reported third-trimester abortions in Georgia by comparing the reported information with actual medical records for each case.[6] Upon reviewing 86 third-trimester induced abortions reported to the Georgia Department of Health and Human Services in 1979 and 1980, the authors found that the vast majority of the abortions were misreported. Only three procedures could be verified as actual third-trimester induced abortions; 58 of those reported were actually fetal deaths in utero, and 15 more were first- or second-trimester abortions that had been misclassified as third-trimester. The researchers concluded that the correct rate of third-trimester abortions for Georgia in 1979 and 1980 was 4.3 per 100,000 total abortions, rather than the rate of 123.1 per 100,000 abortions reported by the state's department of health.

Abortion Reporting

As of January 1998, 48 states, the city of New York[*] and the District of Columbia collect data on induced abortions.[†] The two nonreporting states, California and Oklahoma, have abortion reporting statutes on the books that are not currently in effect due to legal actions taken against related abortion statutes.

Laws

While 40 states and New York City collect abortion data as required by state statute, these laws vary. In 35 states and New York City, induced termination of pregnancy reporting is required specifically by statute (see Table 1). Overall, the laws are similar; by and large, they require every hospital or facility, or attending physician, to file a report regularly on each abortion performed, usually within a few days of the procedure or on a monthly basis. These laws mandate that abortion reports be submitted to the state department of health, state registrar or state vital statistics officer, and that the agency in turn publish the statistics on a regular basis.

Approximately half of the state laws specify that the department of health or a related agency will prescribe and provide the abortion reporting form, and several states require that the form be similar to the U.S. standard suggested by CDC. Virtually all of the statutes include a confidentiality provision—either emphasizing that the data collected are for statistical use only and may be published in aggregate only, or, at a minimum, mandating exclusion of the patient's or provider's name on the reporting form or in the published report.

Four additional states—Hawaii, New York, Rhode Island and Virginia—are legally obligated to collect abortion data under broader fetal death reporting statutes, rather than under laws specific to abortion. The Colorado vital statistics agency, meanwhile, collects abortion data in accordance with its death certification statute, which does not single out fetal death or abortion.

Regulations

Three states—Arizona, Connecticut and Washington—are obligated to collect abortion data solely by regulations issued by their state health agencies (Table 1). Regulations in all three echo the typical reporting statute. Nineteen more states have regulatory policies that accompany their abortion or fetal death reporting statutes. Such regulations typically reinforce the provisions put forth in the state statute and provide administrative guidance for the reporting system. For example, regulations might enumerate exactly what is required on the reporting form, discriminate between requirements for different types of medical facilities or elaborate on confidentiality provisions.

Voluntary Reporting

Five states and the District of Columbia collect abortion data on a voluntary basis, and their health departments provide forms and publish the data—even though no statute or regulation requires that abortions be reported (Table 1). New Jersey and West Virginia cite broad state health statutes as providing legal authority for a state health official to collect abortion-related data, while in Alaska, Maryland, New Hampshire and the District of Columbia, the health departments do not rely on legal authority.

State Data Collection

All states that collect abortion data utilize standardized forms, and most require a separate form for each procedure. The forms largely solicit the same baseline data as does the U.S. Standard Report of Induced Termination of Pregnancy: information on the facility (name or address, city and county); demographic information on the patient (her age, marital status, race, general educational level, and city, county and state of residence); medical information on the patient (date of last normal menses and number and results of previous pregnancies); information on the procedure itself (date of termination, clinical estimate of fetal gestation and method of termination[‡]) and the names of the attending physician and person completing the report.[§]

However, state forms tend to deviate from the U.S. standard in two ways. Many states do not require the same level of detail as the standard form on those items that might identify the facility, patient or attending physician—only 23 states[**] and New York City, for example, require the patient's residential zip code, and only 28 states[††] and New York City request information identifying the attending physician. While all but three reporting areas[‡‡] request information on the type of procedure used, only 17 states,[§§] New York and the District of Columbia include "medical (nonsurgical)" in the list of abortion procedures.

Conversely, many states require more information than that required in the U.S. standard form. Twenty-seven states,[*†] for example, inquire about abortion-related complications, and several ask for additional information on the fetus, such as fetal viability, abnormality, length or weight. Nine states[*‡] ask the reason for the abortion, and seven[*§] request information on the woman's contraceptive history.

Six states and the District of Columbia do not use a separate form for each procedure. Colorado, New Jersey, Texas and West Virginia, which require the same basic information on each abortion as does the U.S. standard form, record abortions in logs that are submitted to the state agency on a regular basis. In Florida, Massachusetts and the District of Columbia, abortions are reported to health agencies in aggregate on a monthly or quarterly schedule.

National Data Collection

Annually, CDC contacts state vital statistics agencies to request certain data tabulations from the previous year. On a voluntary basis, states then submit aggregate data to CDC in the form of the requested tabulations, or as closely as possible, based on the state's available data. In 1995, the most recent year for which CDC data are available, the agency requested data on age

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[*] New York City maintains its own vital statistics systems and policies, which are separate and distinct from the rest of New York State.

[†] In 1996 and 1997, The Alan Guttmacher Institute (AGI) compiled state abortion reporting requirements under grant no. 000057 from the Department of Health and Human Services (DHHS), as part of the department's interest in assessing the accuracy of pregnancy data in the United States. To obtain reporting information from the states, AGI sent state vital statistics officers a copy of the state reporting law from AGI files and asked the officers to verify that the law is current, and, if not, to send AGI a copy of current law. The officers were also asked to send AGI a copy of any current regulations and reporting forms. Parts of this article are based on information gained during that effort; however, this report is neither funded by nor represents the views of DHHS.

[‡] Suction curettage; medical (nonsurgical) abortion; dilation and evacuation; intrauterine instillation; sharp curettage; hysterotomy or hysterectomy; and any other method.

[§] A chart detailing which of the 25 elements from the U.S. Standard form are used by each of the 52 jurisdictions examined in this article is available from the author.

[**] AL, AR, CO, DE, GA, ID, IL, IN, MD, MO, NC, ND, NH, NY, NV, OH, OR, SC, SD, TN, UT, VT, VA.

[††] AL, AZ, CT, GA, HI, ID, IL, IA, IN, KS, LA, ME, MI, MS, MO, MT, ND, NE, NV, NY, OH, PA, RI, SD, TN, UT, VT, WA.

[‡‡] IL, IA, WI.

[§§] AK, DE, KS, KY, ME, MI, MO, NC, NE, NH, NJ, OH, SD, TX, UT, WA, WY.

[*†] AZ, CT, GA, HI, ID, IL, IN, LA, MA, MD, MI, MN, MS, MT, NC, ND, NE, NY, OH, OR, PA, RI, SD, UT, WA, WI, WY.

[*‡] AZ, FL, IL, LA, NE, NY, PA, UT, WV.

[*§] LA, MN, NE, NH, OH, OR, UT.

Table 1. Abortion reporting, by jurisdiction

Jurisdiction	Type of reporting			
	Mandatory			Voluntary
	Abortion statute	Fetal death statute	Regulatory policy	
Alabama	X			
Alaska				X
Arizona			X	
Arkansas	X*			
California				
Colorado		X†		
Connecticut			X	
Delaware	X			
District of Columbia				X
Florida	X*			
Georgia	X*			
Hawaii		X		
Idaho	X*			
Illinois	X*			
Indiana	X			
Iowa	X*			
Kansas	X			
Kentucky	X			
Louisiana	X			
Maine	X			
Maryland				X
Massachusetts	X			
Michigan	X			
Minnesota	X*			
Mississippi	X*			
Missouri	X*			
Montana	X			
Nebraska	X			
Nevada	X*			
New Hampshire				X
New Jersey				X‡
New Mexico	X*			
New York		X		
New York City	X			
North Carolina	X*			
North Dakota	X*			
Ohio	X*			
Oklahoma				
Oregon	X*			
Pennsylvania	X			
Rhode Island		X*		
South Carolina	X*			
South Dakota	X			
Tennessee	X			
Texas	X*			
Utah	X			
Vermont	X			
Virginia		X*		
Washington			X	
West Virginia				X‡
Wisconsin	X			
Wyoming	X			

*A regulatory policy guides abortion data collection in addition to state statute. †Abortion reporting is done in accordance with the state's death certification statute. ‡A broad health statute provides legal authority for abortion-related data collection.

of woman (younger than 15, 15, 16, 17, 18, 19, 20–24, 25–29, 30–34, 35–39, and 40 and older), weeks of gestation (less than or equal to 6 weeks, 7 weeks, 8 weeks, 9–10 weeks, 11–12 weeks, 13–15 weeks, 16–20 weeks, and 21 weeks or greater), type of procedure (suction curettage, all curettage, intrauterine saline instillation, prostaglandin instillation, hysterectomy or hysterotomy, other, unknown), race, Hispanic ethnicity, marital status, previous live births and abortions, and state of residence. As in previous years, CDC surveyed abortion providers in nonreporting states to estimate the number of abortions performed in those states.

Discussion

To a great degree, a national system for collecting data on induced termination of pregnancy is in place, and, by and large, states have moved to adopt federal standards that aim to make data complete and comparable across state lines. However, there remains considerable variability among state laws, policies, forms and systems, and this variability inevitably affects CDC's ability to determine accurately even the total number of abortions performed each year. While state reporting has improved over the years—and three states installed reporting systems for the first time in 1997—AGI reported 13% more abortions nationwide than did CDC in 1995,[7] the latest year for which comparable abortion data are available.

This variability also exacts a toll on CDC's ability to answer specific questions about abortion in the United States. As demonstrated by the review of state reporting forms, there are considerable differences among states that do require abortion reporting in terms of the information they actually collect. Furthermore, for the information reported to the states, there often are problems with data completeness. For example, in CDC's 1995 state-level surveillance report, data on specific variables are missing for a number of states. To better assess the quality of state data, especially for small or sensitive groups, more research like the Georgia study is needed.

At the same time, it is important to understand that the information available to CDC is limited to the specific pieces of data that the agency requests from the states. For example, in 1995, in keeping with past years, the agency requested aggregated tabulations on nine variables, with some limited cross-tabulations. Therefore, the agency does not have access to state-collected abortion data in a record-by-record format, and it cannot then spontaneously answer questions about individual cases or new variables.

As a result of these data limitations, much of the information recently sought by decision-makers engaged in the "partial birth" abortion debate is currently out of CDC's grasp. Detailed information on late-term abortions is unavailable because the relatively small number of abortions beyond 20 weeks are aggregated into one gestational category. Data on certain procedures—including dilation and extraction, the medical procedure that most closely approximates characterizations of "partial-birth" abortion—are also unavailable because states and CDC collect data under broader categories.

Similarly, current limitations cast doubt on the federal government's ability to rely on existing data to responsibly award the "illegitimacy bonuses" authorized in the federal welfare reform law: Doing so would presumably require accurate, complete and consistent data that is comparable across the years—which simply do not now exist.

Finally, the existing abortion surveillance system poses challenges to public health officials in their quest to accurately trace the use of new, nonsurgical abortion techniques. Inclusion of the new techniques on a significant number of state forms demonstrates a sensitivity to the issue on the part of many state vital statistics officers. However, ensuring reporting by all new providers will undoubtedly require increased education and outreach efforts.

While some data limitations may be intrinsic to abortion—and no system is perfect—the quality of CDC's information is primarily compromised by the unevenness of reporting in the states. Policymakers need to assess the value they place on accurate abortion statistics and match information needs with resources. If accurate abortion data are as necessary to policymaking as recent debate suggests, steps need to be taken to bolster the existing systems. Doing so first requires further research into the limitations of the current systems and data, and a significant will to improve state-level data collection and management.

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Campaign for Abortion Pill Supporters seek tests by FDA of French drug for use in U.S.

[NASSAU AND SUFFOLK Edition]

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Supporters of the French abortion pill RU486 are beginning an aggressive campaign to bring the drug to the United States, but abortion opponents are criticizing the effort as largely symbolic.

"We need to increase the demand for the drug to be available in this country," said Joanne Howes, a director of the Reproductive Health Technologies Project of Washington, D.C., which is spearheading the drive to introduce the RU486 pill. "Women should have all options, and it is an outrage that this method to terminate a pregnancy is not available to them."

While some proponents acknowledge that the pill may have some drawbacks when compared to surgical abortion procedures, they urge its acceptance if only to send a message that more research into reproductive medicine is wanted in the United States.

However, opponents who claim the pill is potentially unsafe are confident that the Bush administration's anti-abortion position will keep it from being tested and licensed here.

"Both sides have really dug their heels in on this one; there is a lot of symbolic value in how this really comes out," said Gary Bauer, a former White House adviser on domestic policy to Ronald Reagan and now president of the Family Research Council, which opposes abortion.

Bauer said that if Bush would support Food and Drug Administration licensing of the pill, "he would find himself in the middle of a gigantic controversy." Currently, the FDA will not allow mail-order importation of the drug. There is no pending application by pharmaceutical companies for its use.

The drive to step up debate about the pill this summer, which included a Manhattan news conference yesterday, comes as Roussel Uclaf, the French manufacturer of RU486, plans to apply for a license to bring it to Great Britian this fall in hopes of having it available to women there by late 1991. Supporters hope that this change in position by Roussel's West German parent, Hoechst A.G., - which previously had indicated it would not allow the drug to go to other countries - will make it more likely the firm would be willing to allow the pill to be licensed here if the political climate became more hospitable.

"I see a logical succession of events which starts with the pill first entering England. That will have a lot of consequences," said Dr. Etienne-Emile Baulieu, the French scientist who invented the chemical compound.

Baulieu said in a recent interview that $50 million to $100 million is available from U.S. supporters, which he declined to identify, to test the pill and to set up a non-profit organization with clinics that would distribute it to women if the drug were licensed. {***The following appeared in city edition: "It is certainly good but not technically better than suction abortion. It is different psychologically. It gives a woman more choice," Baulieu said. ***}

By targeting the medical community, Congress, women's groups and the media, proponents of the pill say they hope to pressure the pharmaceutical industry and the Bush administration to test and license the drug. The key to their success, Howes said, may be to stress other possible medical benefits of RU486, such as in treatment for breast cancer, and to cast the issue in "freedom of research" terms. The drug has had limited clinical tests for use as a breast-cancer treatment, but there have been no conclusive results.

However, even if abortion-rights advocates were to overcome the considerable obstacles raised by the anti-abortion lobby, the pill's supporters say its use as an abortion pill would still be at least five to six years away because of the testing process.

RU486 was developed by Roussel in 1980 and approved for use in France in 1988. Since then, 44,000 women have used to the pill to terminate first trimester pregnancies. The drug is most effective when used within three weeks of a missed period.

The pill interferes with progesterone, a hormone that stimulates the uterus to nourish the embryo. The pill must be followed up several days later with injections of another drug that causes the uterus to contract and expel its contents, causing menstruation to begin.

According to Dr. Elisabeth Aubeny, a French doctor and member of the country's National Consultative Committee on Ethics, there was a 5 percent failure rate, requiring additional treatment. Two women had heart attacks that were not attributed to the drugs, but rather to the process under which the drugs were administered.

Aubeny, who met with reporters in Washington and New York this week as part of the media campaign, said some women consider the pill and injections a more natural process than a surgical abortion. However, critics say the repeated doctor's visits are a drawback, and Aubeny noted another potential psychological problem.

"In these {RU486} cases, the women have to wait at least four to five hours at the hospital following the procedure. And about fifty percent of them see the product of the expulsion."

A major boost to pill supporters came when the American Medical Association recently urged the testing of RU486 to determine whether it can be safer and cheaper than surgical abortion and whether it has other uses.

However, the American Academy of Medical Ethics, a group of physicians that opposes abortion, said there was no need to relax product-liability standards to rush this drug to market if it really were intended for other uses.

"Were it not for the nature of the abortion debate, the conversations concerning this drug would be normal, low key, and we wouldn't see all this hoopla," said Dr. Curtis Harris, president of the academy. "A number of the drugs for AIDS therapy have gone a fast track because there was such a compelling need need for them. There is no compelling need for this drug," he said.

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Abstract (Document Summary)

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The drive to step up debate about the pill this summer, which included a Manhattan news conference yesterday, comes as Roussel Uclaf, the French manufacturer of RU486, plans to apply for a license to bring it to Great Britian this fall in hopes of having it available to women there by late 1991. Supporters hope that this change in position by Roussel's West German parent, Hoechst A.G., - which previously had indicated it would not allow the drug to go to other countries - will make it more likely the firm would be willing to allow the pill to be licensed here if the political climate became more hospitable.

By targeting the medical community, Congress, women's groups and the media, proponents of the pill say they hope to pressure the pharmaceutical industry and the [Bush] administration to test and license the drug. The key to their success, [Joanne Howes] said, may be to stress other possible medical benefits of RU486, such as in treatment for breast cancer, and to cast the issue in "freedom of research" terms. The drug has had limited clinical tests for use as a breast-cancer treatment, but there have been no conclusive results.

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UNITED STATES CONFERENCE OF CATHOLIC BISHOPS

Secretariat for Pro-Life Activities
3211 FOURTH STREET NE • WASHINGTON DC 20017-1194 • 202-541-3070 • FAX 202-541-3054
EMAIL: PROLIFE@USCCB.ORG • WEBSITE: WWW.USCCB.ORG/PROLIFE

DATE: May 12, 2006

FROM: William Ryan

O 202-541-3200
H 202-686-1824

FOR IMMEDIATE RELEASE

"HOLLY'S LAW" STILL NECESSARY TO PROTECT WOMEN FROM RU-486

WASHINGTON—The U.S. Food and Drug Administration (FDA) convened a public workshop in Atlanta on May 11 in response to women's deaths from the abortion drug RU-486, also known as "Mifeprex." It was co-sponsored by the Centers for Disease Control (CDC) and the National Institutes of Health.

Five American women have died from infections after undergoing RU-486 abortions, and another died from an undiagnosed ruptured ectopic pregnancy. Over 800 others have suffered serious or life-threatening adverse health effects. Women in Canada, Sweden and the United Kingdom have also died after taking RU-486.

Deirdre A. McQuade, Director of Planning and Information at the USCCB Secretariat for Pro-Life Activities, attended the event and observed: "Women seeking elective chemical abortions remain at risk with RU-486 on the market."

"We continue to call for the passage of Holly's Law to temporarily suspend FDA approval of RU-486 while its approval process is reviewed," Ms. McQuade said.

"Holly's Law" (H.R. 1079) is named in memory of Holly Patterson, a young California woman who died from septic shock after undergoing an RU-486 abortion.

"The CDC workshop is a constructive step, but no substitute for the provisions in Holly's Law, as it neither addresses the distinct risks posed by RU-486 nor offers any immediate protection of women's lives," Ms. McQuade said.

# # # # #

06-096
CNS,RNS,CRUX,SECULAR

To: Mark E. Souder, (IN-03) Chairman
Members of Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
United States House of Representatives
109th Congress

From: Monty L. Patterson

Date: June 12, 2006

Re: Query Concerning Susan Wood's Testimony
Hearing Entitled "RU-486 – Demonstrating a Low Standard for Women's Health?"

I question if there are ethical issues and a potential conflict of interest surrounding Susan F. Wood, PhD, testifying at the Subcommittee Hearing on May 17, 2006. Susan Wood, former FDA Assistant Commissioner for Women's Health, failed to state affiliations with the pro-abortion advocacy organizations which she currently represents.

Susan Wood is currently a Senior Policy Advisor to the Reproductive Health Technologies Project (RHTP). This organization, founded in 1988 by Marie Bass, a former political director of the National Abortion Rights Action League and Joanne Howes, a former lobbyist for Planned Parenthood Federation of America, spearheaded an aggressive campaign to bring RU-486 to the United States prior to FDA approval. As an abortion-rights advocacy group, they have targeted the medical community, Congress, women's groups, the media and the general public to build support for RU-486 in this country today. RHTP has formed critical alliances with the abortion advocacy community such as Gynuity Health Projects, IPAS, the National Abortion Federation, and the National Women's Health Network. Following her FDA resignation, with support from the Open Society Institute, RHTP launched the Dr. Susan Wood: FDA Hero Speaking Tour to pro-choice abortion groups and providers such as Planned Parenthood, National Abortion Rights Action League (NARAL), American College of Obstetrics & Gynecology (ACOG), and Family Planning Advocates.

Without disclosing her affiliation with RHTP, it is my opinion that Susan Wood's testimony lacked both credibility and professionalism. As a professional, she did not display an ethical responsibility to society, her colleagues nor herself. Moreover, Susan Wood does not have formal training as a medical doctor. She is a Doctor of Philosophy in Biology. Although her scientific training as a PhD in Biology is not representative of a medical doctor, Planned Parenthood of America's website displays a "Meet Dr. Susan Wood" narrative which implies her credentials are in the medical profession. Seemingly, Susan Wood has allowed an organization which supports her to knowingly misrepresent her credentials. Furthermore, by continuing to use her former FDA title without disclosing her current affiliations and bias to the pro-abortion organizations which she now represents, Susan Wood exploits that official capacity for professional and personal benefit.

Susan Wood's stated core commitment, to improving and advancing women's health is troublesome, in light of the fact, she challenges credible scientific and medical opinion that RU-486 when used for early medical pregnancy termination may predispose healthy women to serious or lethal infections by impairing the innate immune response. In her testimony, she states, "Questions have been raised about whether mifepristone (RU-486) is involved through suppression of the immune system. This is a question to be studied, but at this point does not seem to be a compelling mechanism." I question Susan Wood's authority to make such statements as a non medical professional.

Still, the most troubling consequence of this testimony is that a pro-choice advocate like Susan Wood is eroding the quality of advice to policymakers and the general public in a manner that is not serving the best interest of women's health. Susan Wood, herself, testifies, "Please do not allow politics to trump science once again when the health of women is at stake." Yet, Susan Wood plays politics with science. Her political quest in the name of science is trumping the safety, health and welfare of women.

Respectively Submitted,

Monty L. Patterson

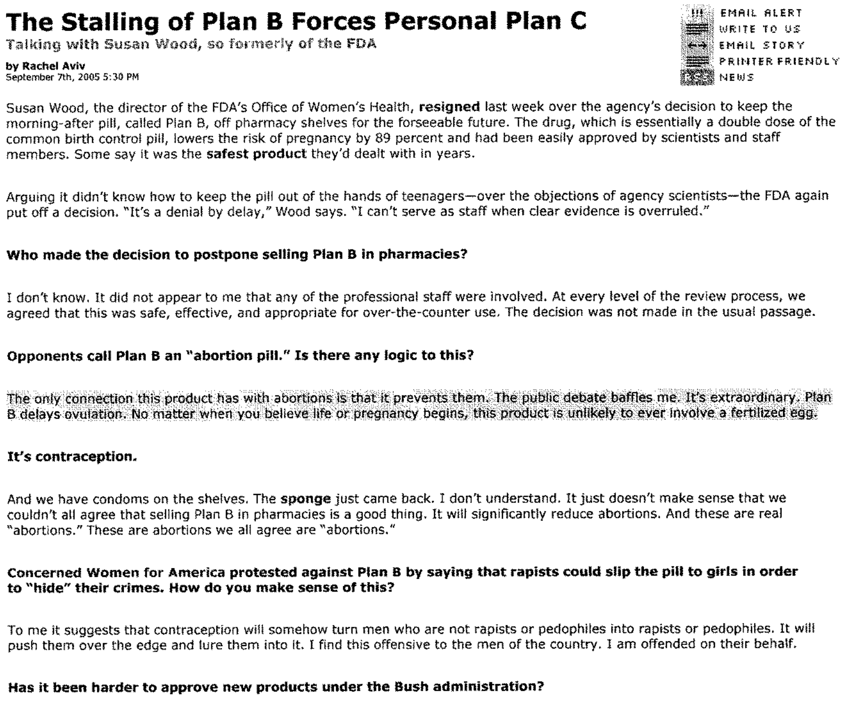
Monty L. Patterson

I regret to tell you that I am leaving the FDA, and will no longer be serving as the Assistant Commissioner for Women's Health and Director of the FDA Office of Women's Health. The recent decision announced by the Commissioner about emergency contraception, which continues to limit women's access to a product that would reduce unintended pregnancies and reduce abortions is ***contrary to my core commitment to improving and advancing women's health.*** *I have spent the last 15 years working to ensure that science informs good health policy decisions. I can no longer serve as staff when scientific and clinical evidence, fully evaluated and recommended for approval by the professional staff here, has been overuled. I therefore have submitted my resignation effective today.*

I will greatly miss working with such an outstanding group of scientists, clinicians and support staff. FDA's staff is of the highest caliber and it has been a priviledge to work with you all. I hope to have future opportunities to work with you in a different capacity.

Sincerely,

Susan



The Stalling of Plan B Forces Personal Plan C

Talking with Susan Wood, so formerly of the FDA

by Rachel Aviv
September 7th, 2005 5:30 PM

Susan Wood, the director of the FDA's Office of Women's Health, **resigned** last week over the agency's decision to keep the morning-after pill, called Plan B, off pharmacy shelves for the forseeable future. The drug, which is essentially a double dose of the common birth control pill, lowers the risk of pregnancy by 89 percent and had been easily approved by scientists and staff members. Some say it was the **safest product** they'd dealt with in years.

Arguing it didn't know how to keep the pill out of the hands of teenagers—over the objections of agency scientists—the FDA again put off a decision. "It's a denial by delay," Wood says. "I can't serve as staff when clear evidence is overruled."

Who made the decision to postpone selling Plan B in pharmacies?

I don't know. It did not appear to me that any of the professional staff were involved. At every level of the review process, we agreed that this was safe, effective, and appropriate for over-the-counter use. The decision was not made in the usual passage.

Opponents call Plan B an "abortion pill." Is there any logic to this?

The only connection this product has with abortions is that it prevents them. The public debate baffles me. It's extraordinary. Plan B delays ovulation. No matter when you believe life or pregnancy begins, this product is unlikely to ever involve a fertilized egg.

It's contraception.

And we have condoms on the shelves. The **sponge** just came back. I don't understand. It just doesn't make sense that we couldn't all agree that selling Plan B in pharmacies is a good thing. It will significantly reduce abortions. And these are real "abortions." These are abortions we all agree are "abortions."

Concerned Women for America protested against Plan B by saying that rapists could slip the pill to girls in order to "hide" their crimes. How do you make sense of this?

To me it suggests that contraception will somehow turn men who are not rapists or pedophiles into rapists or pedophiles. It will push them over the edge and lure them into it. I find this offensive to the men of the country. I am offended on their behalf.

Has it been harder to approve new products under the Bush administration?

Rulemaking and regulation has slowed—in most cases, but not all cases. I'm trying to avoid—I don't want to be someone who says it was politicized. I don't know. I wasn't consulted. I wasn't in any discussions. I wasn't in the room. That's part of the problem. They wouldn't consult the director of the Office of Women's Health for such a decision.

Did you intend for your resignation to be politically symbolic?

The decision was a personal one. I didn't expect it to generate this kind of interest. Now that it has, I have to say I hope it serves some good. The FDA needs to make its decisions based on science. They need to stick with the evidence. I believe there's quite a consensus on the acceptability of this product. The public reaction has been almost uniformly favorable. The conservative press has gone silent.

Do you know what you'll do next? No. I don't follow the advice I give to other people, which is to always line up a job before you give up a current one. I resigned without a parachute.

Choice! Magazine spoke with Wood about the FDA, her decision to leave, and her own plan B — educating the country about the importance of sound science in making decisions about health care.
The Office of Women's Health was not directly involved with the decision on EC, which was handled by the Center for Drug Evaluation and Research. What kind of relationship did you have with the departments that were involved?

When different issues would come up at the different centers, they would call upon us or we would invite ourselves to the table to be part of the discussions.

So, in the case of Plan B, you weren't invited to the table?

Well, not at the highest levels. At the level of the professional staff, they didn't need us to do the review of the data. They were perfectly capable of doing that. They did keep us apprised. We were aware of what was going on. As the advisory committee was being planned, we stayed in touch with what was happening, in an informal way.

Did the process seem to be on the up-and-up at the time?

There had always been concern — an awareness — that [over-the-counter status for EC] might raise a few eyebrows. But internally it was handled fairly, routinely, and thoroughly. It wasn't until *after* the advisory meeting when things seemed to be going down an unusual path.

In your time at the FDA, had you ever seen anything like what happened with EC?

No, and frankly, people who have been at the agency a lot longer than I had were pretty astonished.

Plan B had been stalled for a long time. Had you considered resigning at any other point in the process?

The main point was in May 2004 [when the FDA first rejected over-the-counter status for EC]. I was still not happy, but at that point I felt two things.

First, that the people who were on the scientific professional staff were still part of the conversation. They had lost and were upset, but they were still in there swinging, so to speak. They knew what [information] was coming down as it was coming down.

Second, I believed Steve Galson [the acting director of the FDA's Center for Drug Evaluation and. Research], in that he thought we would be getting [EC] approved in about six or eight months, depending on when [Barr Pharmaceuticals, the manufacturer of Plan B] came back with their application, and that this would be a way toward some form of approval. It would not be perfect but it would be partway there, and that would be a good thing.

But [in August], when [Plan B] hit that wall again, it was clear that the professional staff had no involvement and that this was a way to say no without actually saying no.

Now that you've gone, who is left to advocate from inside the FDA?

Many good people at FDA are still there. The Office of Women's Health is still there. I hope it will be able to continue the good work it was able to do before. People in the review divisions are still there, not just in the reproductive division, but elsewhere.

My concern is that either through demoralization of the staff or the difficulty of recruiting new staff under these circumstances, this could ultimately do some long-term damage. I hope not.

How do you see your role now?

For the near term, I'm trying to take the message to people around the country, from different walks of life, of how important it is that we make our health policy decisions based on science and medicine and not on anything else. I'm not going into the issues of what happened in terms of the politics, because I wasn't part of that. I'm stressing how important it is — from individual health decisions, in terms of reading a medicine label, to larger public health decisions, like decisions made by physicians — that we are able to count on the information being provided by the FDA as being accurate and based on science.

The FDA is really admired and considered the gold standard around the world. That's something that we should be proud of and grateful for, and we have put that at risk — which, in my mind, is really unacceptable. If I can communicate that to people, people can take the next step, which is to insist that we do better, insist on good government decision making, and competent governance and that our health decisions be based on science and medicine.

You're doing this work in conjunction with the Reproductive Health Technologies Project**, a nonprofit organization that is working to get EC available over the counter for U.S. women. Tell us more about that.**

We're trying to raise foundation money and other donations to make it feasible to go out to communities around the country. I think it's important that we get beyond the Beltway, beyond the usual audiences. I've spoken at medical schools, law schools, grassroots organizations, and women's groups, people who care about these issues from different perspectives, to get them involved.

Laura Lambert is a writer and editor in the PPFA Editorial Services Department.

You can help Dr. Wood keep the Plan B story alive--and support science-based decision making and the health of women and their families! Since her courageous resignation six months ago from a top position at the FDA, with sponsorship from the Reproductive Health Technologies Project, Dr. Wood has been traveling the country sharing her concerns about the FDA putting politics before science. She has inspired young people, scientists and policymakers with her call to make emergency contraception widely available to those who need it most. Your gift will support Dr. Wood's outreach efforts to motivate individuals to hold policymakers and elected officials accountable for the politicization of science.

Dr. Wood

I. What was your position at the FDA?
II. The Women's Health Subcommittee is responsible for policy related to women's health issues, correct?
III. So at the FDA, you were involved with policy, not the scientific end of things, necessarily?
IV. Were you normally (more often than not) involved in the drug-approval process?
V. In what capacity?
VI. Since your resignation, you have engaged in a speaking tour, correct?
VII. What has been the central message of your talks? (base our medicine decisions on science, not politics)
VIII. So you oppose the involvement of politics in the drug approval process?
IX. Why? (Hopefully, she will say scientists and drug companies are better able to make decisions about drugs than politicians are).
X. Who is better able to make a decision about the marketing of a drug—a drug maker or a politician?
XI. Who should be involved in the drug approval process?
XII. Do you have proof that there was any politics, or politicians, involved in the decision not to allow the marketing of Plan B over the counter?
XIII. If there was evidence that it was, for example, President Bush's decision not to allow the marketing of Plan B in the U.S., would you agree with President Bush's interference with the drug approval process? Why or why not?
XIV. If a company wants to file a New Drug Application, should President Bush, or any president, prevent that application from being filed, for any reason? What if they don't want to file a New Drug Application? Should a president interfere with their decision not to do so? Why or why not?
XV. Should the Department of State be involved in the drug approval process? Why or why not?
XVI. Since you disavow the interference of politics in the marketing of drugs, when Roussel Uclaf discontinued the production of Mifepristone, you would disavow the French Health Minister's Demand that they put the drug back on the market, correct?
XVII. Since you disavow the interference of politics in the marketing of drugs, you disavow President Bill Clinton directing the Secretary of Health and Human Services to apply pressure to Roussel Uclaf to market the drug in the United States, correct?
XVIII. Since you disavow the interference of politics in the marketing of drugs, you disavow the State Department under President Bill Clinton applying diplomatic pressure to Roussel Uclaf to bring RU-486 to the United States, correct?
XIX. Since you disavow the interference of politics in the marketing of drugs, you disavow the State Department under President Bill Clinton enlisting the help of the French and German governments to apply diplomatic pressure to Roussel Uclaf to market RU-486 in the United States, correct?

XX. In an interview with *Choice Magazine*, which is an online publication of Planned Parenthood—the largest abortion provider in the U.S.—you fielded this question:

Now that you've gone, who is left to advocate from inside the FDA?

To which you responded:

"Many good people at FDA are still there. The Office of Women's Health is still there. I hope it will be able to continue the good work it was able to do before. People in the review divisions are still there, not just in the reproductive division, but elsewhere.

My concern is that either through demoralization of the staff or the difficulty of recruiting new staff under these circumstances, this could ultimately do some long-term damage. I hope not."

Advocate for what? What type of "people" are you referring to?

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When Politics Defeats Science

By Susan F. Wood
Wednesday, March 1, 2006; A17

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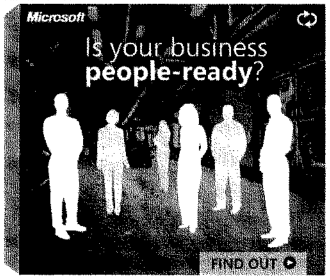

Since my resignation six months ago as assistant commissioner of women's health at the Food and Drug Administration, I have been traveling around the country meeting with men and women, fellow scientists and health care professionals. I have shared my concerns that our federal health agencies seem increasingly unable to operate independently and that this lack of independence compromises their mission of promoting public health and welfare.

At every stop I am reminded that whether it is the environment, energy policy, science education or public health, the American public expects our government to make the best decisions based on the best available evidence.

Yet, at a recent hearing of the House Appropriations subcommittee on labor, health and human services, we saw once again that this is not happening. Reps. Sam Farr (D-Calif.) and Rosa DeLauro (D-Conn.) questioned FDA acting commissioner Andrew C. von Eschenbach about the delay in approving the application to make Plan B emergency contraception available over the counter to women 17 and older. Von Eschenbach responded that the agency was carefully reviewing the thousands of comments received in response to last-minute concerns raised about the feasibility of making the same product available over the counter for most women but keeping it on prescription for young teens. This exchange confirmed my suspicion that, like his predecessor, von Eschenbach is unable or unwilling to let the science and the scientists guide FDA policy and decisions, and that the real answer as to whether the FDA will allow Plan B over the counter for those 17 and older is no.

Time and again in my travels I am asked, "What happened to derail Plan B?" I have to answer honestly that I don't know. The manufacturer agreed to take the "controversial" issue of young teens' access to emergency contraception off the table in 2004; now we are talking only about adult access to safe and effective contraception. Over 98 percent of adult women have used some form of contraception. So what is the objection?

Perhaps it is that posed by a small but vocal political minority that insists on labeling emergency contraception as abortion, or at least confusing the two. One of the main questions I hear is, "Does this pill cause an abortion?" In fact, the only connection this pill has with abortion is that it has the potential to prevent the need for one. Emergency contraceptive pills work exactly the same way as other birth control pills, and they do not interfere with or harm an existing pregnancy. Emergency contraception is simply a higher dose of daily birth control pills; it is not RU-486, the "abortion pill." Indeed, emergency contraception has been used as a method to prevent unintended pregnancies for decades by women who had physicians advise them on how many pills in their regular pill pack to take. So people who are comfortable with oral contraceptives as methods of contraception should be just as comfortable with emergency contraception.

Having spent 15 years working for the federal government, nearly five of which were at the FDA, I care deeply about what's happening in the federal agencies, particularly our health agencies. Nearly 25 cents of every consumer dollar is spent on products regulated by the Food and Drug Administration. We count on the FDA for the safety and effectiveness of our medicines, vaccines and medical devices, and for the safety of the blood and food supply. The American public does not want to -- nor should it -- have to think twice about the quality and reliability of information it is getting from the FDA. Its reputation as the international gold standard for regulatory agencies, and as a body that sets the bar very high when it comes to scientific evidence and integrity, is being put at risk over adult access to contraception. Why would the administration risk such a reputation over this?

Von Eschenbach could demonstrate his commitment to the FDA's independence and scientific integrity and help restore staff morale and waning public credibility by stopping the rulemaking process and approving access to Plan B for women 17 and older. Instead, he continues to hide behind a wasteful and pointless bureaucratic process. Congress needs to step in and restore the FDA's independence and its ability to make decisions based on the evidence.

It's been nearly three years since the first application came in to make Plan B emergency contraception available over the counter, so that women, including rape victims, could have a second chance to prevent an unintended pregnancy and the need for an abortion. How many chances have we missed? I still can't explain what is going on here, and why women 17 and older are still denied this product in a timely way. When did adult access to contraception become controversial? And why have we allowed it to happen?

The writer is a former assistant commissioner of the Food and Drug Administration and is a senior policy adviser to the Reproductive Health Technologies Project.

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Major Changes to Cytotec Labeling

- Removes the contraindication and precaution that Cytotec should not be used in women who are pregnant.

  Rationale: The drug is widely used by obstetricians and gynecologists (OB-Gyns) to induce labor, delivery, and is part of the FDA approved regimen for use with mifepristone to induce abortion in pregnancies of 49 days or less

- Clarifies that the contraindication is for pregnant women who are using Cytotec to reduce the risk of non-steroidal anti-inflammatory drug (NSAID)-induced stomach ulcers.

  Rationale: This contraindication now refers to the drug's approved indication, for reducing the risk of NSAID-induced gastric ulcers. It does not contraindicate off-label uses related to practice of medicine.

- Creates a new labor and delivery section of the labeling and provides safety information related to those uses.

  Rationale: 21CFR 201.57.f.7 requires labeling to include drug effect information if a drug has a recognized use for labor and delivery, whether or not the use is stated in the indications section of the label.

- Provides new information that uterine rupture, an adverse event reported with Cytotec, is associated with risk factors, such as later trimester pregnancies, higher doses of the drug, including the manufactured 100 mcg tablets, prior Cesarean delivery or uterine surgery, and having had five or more previous pregnancies.

  Rationale: Risk factors allow physicians to identify patients who may be at greater risk for these adverse events. This information may guide safer use of the drug.